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Mild Cognitive Impairment in Presurgical Deep Brain Stimulation for Parkinson's Disease

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MILD COGNITIVE IMPAIRMENT IN PRESURGICAL DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Arts & Sciences
at the University of Kentucky

By
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ABSTRACT OF DISSERTATION

MILD COGNITIVE IMPAIRMENT IN PRESURGICAL DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE

Although clinically characterized by motor impairments, Parkinson's disease (PD) often affects cognition early in the disease course. Cognitive changes common in PD include visuospatial abnormalities and prominent executive function (EF) deficits, with 30% of individuals eventually developing Parkinson's disease dementia (PDD). Mild cognitive impairment (MCI) has been identified as a transitional state between normal cognition and PDD. A large cohort of individuals with PD at the Kentucky Neuroscience Institute have undergone pre-surgical evaluations for deep brain stimulation, although cognitive performance in this cohort has never been probed. Baseline cognitive performance of this cohort from 2017-2020 was examined to characterize the pattern of cognitive functioning in these individuals. Data from 136 patients were available for inclusion, and 110 were available for MCI analyses. Prevalence of MCI was approximately 20%, with highest agreement between MCI criteria and clinician diagnostic impressions using a cut point of 1.5 standard deviations (SD) below normative values. The memory domain was most often impaired for those with MCI (65.5%), whereas the language domain was least often impaired (20.9%). Areas under the curve (AUC) were accordingly weaker for language domain measures (e.g., Boston Naming Test, AUC=.695) relative to domains such as visual memory (e.g., BVMT-R Delay, AUC=.883) and EF (e.g., D-KEFS Trails Switching, AUC=.829). Results support the use of 1.5 SD below normative values as a cut point for identifying MCI in PD and highlight the need for visual memory measures in PD cognitive evaluations. Results also align with the extant findings of impairment in key domains such as EF in PD-MCI. Further longitudinal investigation is needed to elucidate the impact of pre-DBS PD-MCI on post-surgical cognitive outcomes.

KEYWORDS: Parkinson's Disease, Mild Cognitive Impairment, Deep Brain Stimulation, Cognition

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MILD COGNITIVE IMPAIRMENT IN PRESURGICAL DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE

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DEDICATION

To my family, who have supported and encouraged my love of learning from the beginning; to my friends, who filled the six years of graduate school with fun and laughter; and to my advisors, Dr. David Berry, Dr. Frederick Schmitt, and Dr. Lisa Koehl, and Dr. Jordan Harp for their support and generosity throughout.

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CHAPTER 1. INTRODUCTION

1.1 Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder affecting 572 per 100,000 adults aged 45 or older in North America (Marras et al., 2018). PD is one of the synucleinopathies, neurodegenerative diseases which involve neuronal and glial alpha-synuclein aggregation (Martí, Toloso, & Campdelacreu, 2003). PD affects the basal ganglia, a subcortical system that contributes to motor planning and muscle tone, resulting in the progressive loss of dopaminergic cells in the substantia nigra. As a hypokinetic disorder, PD is defined by two or more of the following motor symptoms: bradykinesia (or hypokinesia), rigidity, resting tremor, and posture/balance disturbance (Davie, 2008; Grant & Adams, 2009). Additional symptoms seen in PD include micrographia, dysarthria, facial masking, gait changes (i.e., freezing, shuffling, and festinating), dysphagia and subsequent sialorrhea, sleep disturbance, orthostatic hypotension, and mood changes. Hyposmia, constipation, and REM sleep behavior disorder have been reported as possible early indicators of the disease that may precede motoric symptoms (Davie, 2008; Grant & Adams, 2009; Martí et al., 2003; Moreau et al., 2007; Zhang, Sun, Wang, Tang, & Xie, 2017).

1.2 Cognitive Changes in PD

PD often affects cognition early in the disease course and perhaps years before motor impairment (Chahine et al., 2016). Those with postural and gait disturbance as their predominant symptoms, relative to tremor, may be particularly vulnerable to cognitive dysfunction (Baba et al., 2017; Martí et al., 2003). Cognitive changes common in PD

include slowed thinking speed and verbal fluency, visuospatial difficulties, worsened attention and memory encoding, mood symptoms such as depression and apathy, and executive dysfunction (Lezak, Howieson, Bigler, & Tranel, 2012; Schoenberg & Scott, 2011).

These cognitive changes implicate frontal systems involved in goal-directed behavior (e.g., planning, organizing, and manipulating information), suggesting frontostriatal dopaminergic dysfunction as a major pathophysiological mechanism of PD cognitive changes (Owen, 2004; Williams-Gray et al., 2007). The effect of dopaminergic dysfunction and depletion in PD cognition is further highlighted by improvement in executive inefficiencies after levodopa administration (Schrag et al., 2017) and worsening following withdrawal (Owen, 2004). Structural changes in the PD brain further implicate frontal functions, including frontal gray matter atrophy (Minkova et al., 2017) and the association of smaller striatal volume with worse phonemic fluency (Ellfolk et al., 2014).

Frontal dopaminergic dysfunction is not the only mechanistic factor affecting cognition in PD, however. Neuronal loss also occurs in other brain areas, such as the nucleus basalis of Meynert, implicating Lewy body pathology, other misfolded proteins such as beta-amyloid, and factors that are less understood including neuroinflammation (Kalia & Lang, 2015). Cholinergic functioning is diminished in PD and PD dementia (PDD), with cholinergic depletion in PDD estimated to be greater than in Alzheimer's disease (Weintraub, Somogyi, & Meng, 2011) resulting in worsened attention and executive functioning (Bohnen et al., 2006). Additionally, other neurological processes are independently known to affect cognition in the aging brain, such as vascular health, and may exacerbate PD-related cognitive changes (Cholerton et al., 2018; Park et al., 2019).

1.3 Parkinson's Disease Dementia

The risk of more severe cognitive deficits increases with age and PD severity (Hanagasi, Tufekcioglu, & Emre, 2017). Dementia or major neurocognitive disorder is broadly defined as impairment in two cognitive domains with functional impairment (American Psychiatric Association, 2013). Point prevalence of PDD is approximately 30%, with a cumulative prevalence over 10 years of 75% (Litvan et al., 2011).

PDD is characterized by neuronal loss, the presence of Lewy bodies (misfolded alpha-synuclein) in the substantia nigra and throughout the cortex (Martí et al., 2003), and marked cortical cholinergic deficits (Klein et al., 2010). AD-like changes such as beta-amyloid plaques, tau tangles, and hippocampal volume loss are present in PDD (Schrag, Siddiqui, Anastasiou, Weintraub, & Schott, 2017). PDD also evidences widespread cortical hypometabolism on FDG-PET (Klein et al., 2010).

1.3.1 Predictors of PDD

Clinical predictors of PDD include male sex, older age, older age at PD onset, more severe parkinsonism, lower educational attainment, and depression (Hu et al., 2014; Korczyn, 2001; Rektorova, 2011). Identified cognitive markers of risk for PDD progression include worse semantic fluency than phonemic fluency and impaired simple visual reproduction (Williams-Gray et al., 2007). These deficits, not typically prominent in PD alone, suggest involvement of posterior areas in producing the more severe impairment of the dementia syndrome. Further characterizing PDD as a 'whole-brain' syndrome rather than just subcortical, as once believed, glucose hypometabolism in the parietal and occipital lobes on FDG-PET has been identified as a significant predictor of PDD (Baba et al., 2017).

The heterogeneity of cognitive predictors implicated in progression to PDD suggests not only dopaminergic depletion in the frontostriatal circuit, but Lewy body accumulation and cholinergic depletion as this circuit receives both dopaminergic and cholinergic innervation (Litvan et al., 2011; Williams-Gray et al., 2007). Further, reduced cholinergic neuron density in the basal forebrain has been observed in individuals with PDD, while even individuals with PD without dementia show decreased cholinergic activity in the posterior cortex (Baba et al., 2017). The impact of diminished cholinergic functioning is additionally supported by improved overall cognition, attention and processing speed, verbal fluency and problem-solving, word recall and recognition, and visuoconstructional ability in individuals with PDD treated with the cholinesterase inhibitor rivastigmine compared to placebo (Emre et al., 2004; Schmitt, Farlow, Meng, Tekin, & Olin, 2010; Weintraub et al., 2011). Additional neurotransmitters, such as glutamate, are also implicated: use of the NMDA receptor antagonist memantine has led to improvement in attention and processing speed measured via decisional reaction time, as well as immediate and delayed word recognition accuracy, in individuals with PDD (Wesnes, Aarsland, Ballard, & Londos, 2015). The connections between posterior cortical areas and cholinergic function suggest a broader picture of cognitive dysfunction in PD beyond just dopaminergic dysfunction and associated executive function deficits, especially given reduced cholinergic activity and positive cognitive response to cholinesterase inhibitors (i.e., donepezil, galantamine, and rivastigmine) evident in PD without dementia (Bohnen et al., 2006; Wang et al., 2015).

1.4 Deep Brain Stimulation

Deep brain stimulation (DBS) is a surgical treatment option for PD approved for use in the US since 2002. DBS allows controllable and reversible electrical stimulation to be delivered to deep brain structures. This stimulation in the context of PD interferes with the defective neural signals in the basal ganglia motor pathway. DBS, particularly of the subthalamic nucleus (STN) and globus pallidus pars internus (GPi), has proven to be an effective and safe treatment for the motor symptoms of PD (Dafsari et al., 2016; Groiss, Wojtecki, Südmeyer, & Schnitzler, 2009). Particularly, patients with motor fluctuations or tremor poorly managed by medication or for whom medications produce adverse side effects may be suitable candidates (Bronstein et al., 2011).

1.5 Deep Brain Stimulation and Cognition

The effects of DBS on cognitive functioning have been increasingly explored in the literature, although the results are still mixed. Minimal declines in global cognition have been observed for patients pre- vs. post-DBS (Combs et al., 2015; Parsons, Rogers, Braaten, Woods, & Tröster, 2006; Tang et al., 2015); alternatively, more variable global cognitive performance has been reported post-STN DBS when compared to PD patients on medication alone (Rinehardt et al., 2010). No difference or small improvements following STN DBS have been observed on measures of attention, psychomotor speed, visuospatial skill (Parsons et al., 2006), working memory, and immediate verbal recall (Tang et al., 2015). More commonly, however, mild to moderate declines in various cognitive domains have been reported following STN DBS, possibly due to changes in the fronto-striatal pathway (Halpern, Rick, Danish, Grossman, & Baltuch, 2009; Rinehardt et al., 2010). Consistent with this proposed area of change, declines have been observed on executive

tasks following STN DBS (Parsons et al., 2006): Relative to PD patients on medication alone, STN DBS patients demonstrated poorer performance on executive tasks across a two-year period (Tramontana et al., 2015). In a longitudinal analysis, declines in executive functioning post-STN DBS were noted across an 11-year period (Rizzone et al., 2014). Postoperative STN DBS patients have also been shown to make riskier gambling decisions in the Game of Dice Task than healthy controls or PD patients on medication alone (Brandt et al., 2014), further implicating executive function changes.

Significant postoperative declines have been consistently observed for verbal fluency (Rinehardt et al., 2010; Rizzone et al., 2014). Suggested causes include electrode placement, with more deficits observed for STN vs. GPi; high frequency stimulation (130 Hz); and surgical electrode insertion effects (Gaspari et al., 2006; Højlund, Petersen, Sridharan, & Østergaard, 2017). Declines on word fluency after STN DBS have been noted relative to PD patients on medication alone (Tramontana et al., 2015) as well as relative to preoperative performance (Tang et al., 2015), with declines in the latter group observed both in the acute postoperative phase and months to years following surgery (Borden et al., 2014). Although general cognitive deficits are often more pronounced in older individuals who have been treated for PD for many years (Grant & Adams, 2009), age and disease duration do not appear to be significant moderators in the relationship between DBS and verbal fluency decline (Parsons et al., 2006). Comparing STN to GPi DBS, the former has been associated with worse phonemic fluency (Okun et al., 2009), consistent with the suggestion that DBS targeting the GPi produces fewer cognitive symptoms (Combs et al., 2015).

In meta-analytic review, moderate declines have been observed on tasks of phonemic fluency (d = .51), semantic fluency (d = .73), and overall verbal fluency (d = .64) (Parsons et al., 2006). However, these declines in phonemic and semantic fluency may be smaller than previously thought (d = .36 and d = .48, respectively; Combs et al., 2015). Of note, pre-DBS PD patients tend to exhibit lower phonemic fluency performances relative to semantic fluency (Jaywant, Musto, Neargarder, Gilbert, & Cronin-Golomb, 2014), representing an opposite pattern from that seen post-DBS and suggesting greater postoperative disruption of temporal lobe connectivity.

Given these areas of cognitive decline following DBS for PD, evaluation of cognitive status is an important component of the presurgical examination process.

1.6 Mild Cognitive Impairment

Mild cognitive impairment (MCI) refers to the cognitive state between normal aging and dementia (Flicker, Ferris, & Reisberg, 1991; Petersen et al., 2001). MCI was first studied in the context of Alzheimer's disease. In this area, MCI was characterized by subjective memory impairment (with objective evidence of impairment on cognitive assessment preferable) greater than would be expected based on one's age and education but not to the extent that the individual would meet criteria for Alzheimer's, including a lack of functional impairment (Petersen et al., 2001). Using this original memory-centric criterion, approximately 80% of individuals with MCI were estimated to progress to Alzheimer's disease. This progression was estimated to occur at a rate of 12% per year compared to 1-2% in the general population (Petersen & Morris, 2003).

Although MCI as it affects memory is especially relevant in the context of Alzheimer's disease, MCI has subsequently been divided into the following three subtypes based on the observation that individuals can present with impairment in non-memory (e.g., language, executive function) cognitive domains: amnestic MCI, multiple domain MCI (with md-MCI+a indicating memory impairment), and single nonmemory domain MCI (Roberts & Knopman, 2013). Although individuals with MCI progress to dementia at higher rates than the general population, others maintain their MCI status or appear to revert to normal cognition. While unclear whether recovery to normal cognition (characterizing approximately 20% of those with MCI) represents fluctuations in the dementia process over time or other medical conditions affecting cognition, those who revert still exhibit a greater risk for progression to dementia than those never exhibiting MCI (Abner et al., 2012; Roberts & Knopman, 2013). Risk factors associated with transition and time to transition between normal cognition, MCI, and dementia include presence of APOE4 genotype, vascular risk factors such as tobacco use and high blood pressure, and family history of dementia (Kryscio et al., 2013).

1.7 MCI in Parkinson's Disease

MCI has received increased research attention in the context of PD, with evidence for a preclinical phase with distinct characteristics compared to Alzheimer's disease (Jacobs et al., 1995). An average of 27% of individuals with PD meet criteria for PD-MCI (Litvan et al., 2011). Demographic factors associated with PD-MCI diagnosis include advanced age, greater severity of PD, later disease onset, and lower educational attainment. Even before the greater cognitive burden and functional impairment seen in PDD, PD-MCI is associated with lower quality of life for PD patients (Litvan et al., 2011). Of MCI

subtypes, the single nonmemory domain was thought to be more common in PD (Litvan et al., 2011). However, Goldman and colleagues (2013; 2015) identified the strong presence of multiple domain MCI (md-MCI in over 90% of patients in both studies) compared to single domain MCI (over 7% of patients in both studies) in their samples, with single domain impairments in executive, memory, and visuospatial functioning. Meta-analysis has further highlighted the predominance of multiple domain (prevalence 36%) vs. single domain (prevalence 6%) (Baiano, Barone, Trojano, & Santangelo, 2020).

PD-MCI is often characterized by executive dysfunction (Costa, Caltagirone, & Carlesimo, 2018; Foo et al., 2017; Goldman et al., 2013), consistent with the aforementioned cognitive changes in PD generally. However, verbal and visual memory deficits have also been implicated (Bezdicek et al., 2019; Foo et al., 2017). In their review, Goldman and Litvan (2011) corroborate this heterogeneity, citing studies indicating both executive and memory deficits. Although an investigation by Aarsland and colleagues (2010) reported verbal and visual memory deficits were common among those with PD-MCI, single nonmemory domain MCI (i.e., attention, executive function, and visuospatial abilities) was ultimately more prevalent than a-MCI. It is likely that memory deficits reported by some studies merge retention and retrieval difficulties with executively mediated encoding deficits typical in PD (Goldman & Litvan, 2011). Meta-analysis of cross-sectional cognitive performance in PD-MCI vs. normal cognition indicated large effects for verbal and visual delayed memory, and visuospatial skills, suggesting prominence of these deficits in PD-MCI (Wallace, Segerstrom, van Horne, Schmitt, & Koehl, 2021).

Neuroimaging studies have demonstrated a variety of subcortical differences between individuals with PD-MCI and those with PD without cognitive impairment. These changes include the following: thalamic, caudate, nucleus accumbens, and hippocampal atrophy (Foo et al., 2017), which were associated with executive dysfunction (i.e., performance on the Frontal Assessment Battery, including similarities, phonemic fluency, and go/no-go tasks) and memory difficulties (i.e., delayed verbal memory); and cortical thinning particularly in frontal and temporal lobes (Mak et al., 2015), which was associated with lower cognitive screening scores on the Montreal Cognitive Assessment (Nasreddine et al., 2005). Mildly reduced cholinergic binding throughout the cortex may be seen in addition to the dopaminergic deficits typical of PD, suggesting a neurotransmitter basis for the progression from cognitively normal to MCI to PDD (Klein et al., 2010). This increasing implication of acetylcholine as PD progresses to PD-MCI and PDD is again corroborated by the positive effect of cholinesterase inhibitors on cognition in PD-MCI and PDD (Wang et al., 2015). The heterogeneity of implicated neuroanatomical sites and neurotransmitters that appear to be affected by PD-MCI reflects the increasingly complex picture of cognitive changes in PD in general.

1.8 MCI and Progression to Dementia

PD-MCI is associated with greater risk of progression to PDD. The presence of the single nonmemory domain MCI has been shown to predict conversion to PDD (Janvin et al., 2006). Janvin and colleagues (2006) found that 62% of individuals with PD-MCI progressed to PDD in four years compared to 20% of cognitively normal individuals with PD. By other estimates, approximately 10% of those with PD-MCI will progress to dementia after one year and approximately 29% will progress after five years. However,

as in MCI due to other processes such as AD, some individuals with PD-MCI will maintain their MCI status or clinically appear to revert to normal cognition upon follow-up assessment (Bezdicek et al., 2018).

Cognitive predictors of progression from PD-MCI to PDD have begun to be explored, although longitudinal investigations are limited. Existing evidence suggests that processing speed and working memory performance are predictive of progression from PD-MCI to PDD (Cholerton et al, 2018). Significantly worsened verbal fluency and processing speed, visual problem-solving, verbal encoding, and visual reproduction have also been associated with PD-MCI to PDD progression (Gasca-Salas et al., 2014). Meta-analysis of extant longitudinal investigations of baseline PD-MCI vs. normal cognition demonstrated a moderate effect for executive measures, suggesting that executive function deficit at baseline is associated with dementia progression in those with MCI (Wallace et al., 2021). Ultimately, the heterogeneity of assessments used to identify MCI and the relative lack of longitudinal investigations of PD-MCI remain obstacles in characterizing correlates of progression.

1.9 MCI and Deep Brain Stimulation

Cognitive outcomes of DBS have received much attention in the extant literature, and those meeting criteria for dementia before surgery are known to be poor candidates (Okun, 2012). However, relatively little is known regarding the impact of preexisting milder cognitive deficits or MCI on postsurgical outcome. Accordingly, there are no established guidelines for surgical decision-making for patients with PD-MCI.

Some studies have explored this question, with overall results suggesting DBS is likely safe for patients with MCI. Presurgical MCI does not appear to significantly predict postsurgical short-term (within one year) progression to dementia (Merola et al., 2014), although MCI, regardless of subtype, has been identified as a predictor of PDD in other investigations (Kim et al., 2014). MCI also does not appear to predict indicators of poor outcome, such as postoperative confusion (Abboud et al., 2015). Further, the benefits posed by DBS to motor function and quality of life may outweigh the postsurgical cognitive risk of DBS for someone meeting criteria for MCI (Mills et al., 2019).

However, declines in cognitive function following DBS coupled with presurgical deficits can be concerning for patients. In accordance with non-DBS studies of MCI, patients receiving DBS with MCI at baseline appear to demonstrate greater and earlier postsurgical cognitive deficits compared to those with normal cognition: Median time to PDD development following DBS has been evidenced as 6.03 years for those with MCI and 11.08 years for those with normal cognition (Merola et al., 2014). Similarly, 46.4% of patients with presurgical MCI developed PDD within 6.3 years vs. 22.2% for those with normal cognition (Gruber et al., 2019). Five-year postsurgical mortality rates between those with MCI and normal cognition have also been shown to differ, with Merola and colleagues observing rates of 25% vs. 11.94%, respectively. Limitations of these findings include the inclusion of patients receiving predominantly STN DBS, with limited evidence for GPi DBS, Further, other studies have evidenced no difference on postsurgical mortality between those with baseline normal cognition, PD-MCI, and those meeting criteria for PDD, as well as no difference on postsurgical nursing home admissions between PD-MCI and normal cognition (Park et al., 2020). Investigations into postsurgical impact of MCI

also occur in the context of DBS treatment not halting or reversing the progressive course of PD, with postsurgical dementia reflecting continuing disease (Aybek et al., 2007). Ultimately the extant literature has yet to reach a consensus on the effect of MCI on post-DBS outcomes, specifically whether MCI affects cognition post-surgically above and beyond the disease itself.

Interestingly, impairment in some cognitive domains more than others may be associated with worse post-surgical outcomes. Deficits in attention, evidenced by performance on digit span and letter number sequencing tasks, have been associated with prolonged hospitalization following DBS (Abboud et al., 2015). Performance in the executive function domain has also been predictive of faster decline and higher conversion to PDD following STN DBS (Kim et al., 2014). Clinically, however, patients with baseline PD-MCI pre-surgically may experience less prominent postsurgical declines than those with normal cognition given their already present deficits presurgically, such as in phonemic verbal fluency (Merola et al., 2014). Ultimately, the utility of MCI, and/or a patient's specific domain impairment pattern, in making clinical decisions regarding DBS remains unclear.

1.10 Clinical Criteria for Diagnosing PD-MCI

Given the clinical utility of PD-MCI in identifying patients early who may be at greater risk for progression to PDD, the Movement Disorder Society (MDS; Litvan et al., 2012) developed the first structured criteria for diagnosing PD-MCI to facilitate the systematic study of the construct. Criteria include clinically diagnosed PD and subjective cognitive complaint reported by patient or informer, or observed by the clinician, although

the risk of patients and caregivers over- or under-reporting cognitive complaints is noted. These criteria divide diagnosis into Level I and Level II based on the availability of cognitive assessment data. Inclusion, exclusion, Level I, and Level II criteria are summarized in Table 1.1. The criteria recommended defining impairment as one to two standard deviations (SD) below appropriate test norms, although alternative approaches include identifying impairment via percentile ranges of test scores (Aybek et al., 2007; Chung et al., 2019). Subsequent studies utilizing MDS criteria have explored more specific cut points (e.g., 1.5 SD; Pedersen et al., 2013) and compared different cut points (i.e., 1, 1.5, and 2 SD; Goldman et al., 2013; Lawson et al., 2017). Use of the Level II diagnostic process, with cut point 2 SD below norms and two measures per cognitive domain, yielded high sensitivity (81.3%), specificity (85.7%), positive and negative predictive power values (90.7% and 72.7%, respectively), and overall hit rate (82.9%) for PD-MCI diagnosis (Goldman et al., 2015). Although this 2 SD cut point has demonstrated favorable operating characteristics, studies continue to test a variety of cut points (e.g., 1.5 SD below norms; Chen et al., 2019; Kalbe et al., 2016). There exists little consensus on which cut point to employ consistently in research or clinical practice.

1.11 Outstanding Issues and Current Study

Research has increasingly identified PD-MCI as the clinical syndrome associated with higher rates of progression to PDD. Although the MDS criteria standardize the assessment of PD-MCI and have demonstrated favorable operating characteristics, PD-MCI remains a clinical construct comprised of heterogeneous cognitive deficits. The rates and cognitive profiles of those with PD-MCI who are seeking DBS are also poorly defined. The current study aims to join these areas of PD research by characterizing baseline pre-

Table 1.1 MDS criteria for PD-MCI (Litvan et al., 2012)

Inclusion Criteria	- Diagnosis of PD - Subjective memory complaint - Objective evidence of memory impairment - Largely intact functional activities
Exclusion Criteria	- Diagnosis of PDD - PD not the primary cause of cognitive changes - Comorbid conditions (e.g., anxiety, depression) severe enough to interfere with cognitive testing
Level I (Abbreviated Assessment)	- Impairment on global cognitive abilities scale (e.g., MoCA, DRS) - Impairment on two or more tests of neurocognitive functioning in a limited battery of assessments[1]
Level II (Comprehensive Assessment)[2]	- Neurocognitive assessment using two tests for each of the five relevant cognitive domains - Impairment[3] on two or more tests, either within the same or different domains

Note. PD = Parkinson's disease; MCI = mild cognitive impairment; PDD = Parkinson's disease dementia; MoCA = Montreal Cognitive Assessment; DRS = Dementia Rating Scale.

[1]Limited battery = less than two tests used within the five relevant domains of attention and working memory, executive functioning, language, memory, and visuospatial functioning; or less than these five domains are tested.

[2]Level II assessment allows for MCI subtyping into PD-MCI single-domain (i.e., deficits on two tests within one domain) or PD-MCI multiple-domain (i.e., deficits on one or more test(s) in at least two different domains).

[3]Impairment = performance between one and two standard deviations below appropriate (i.e., age, education, gender, and cultural) norms, decline across repeated testing, or decline from estimated premorbid functioning.

surgical cognitive performance in a sample of patients with PD seeking DBS at the University of Kentucky. Prevalence of PD-MCI per MDS criteria will be identified, as will measures' discrimination ability of PD-MCI vs. normal cognition.

CHAPTER 2. METHOD

2.1 Inclusion Criteria and Variables

Inclusion criteria for this retrospective record review were as follows: 1) completion of presurgical DBS cognitive evaluation; 2) assessment between 2017-2020 following standardization of the DBS presurgical cognitive battery in 2017; 3) diagnosis of idiopathic PD. Patients completing a presurgical DBS cognitive evaluation for diagnoses other than PD were not included (e.g., essential tremor). Of those with PD diagnoses, patients were excluded if presenting with dual diagnoses of atypical PD or PD and essential tremor. The following demographic variables were recorded: age, handedness, ethnicity, sex, education, Hoehn & Yahr (Hoehn & Yahr, 1967) rating on and off dopaminergic medication, levodopa equivalent daily dose (LEDD; Tomlinson et al., 2010; calculated via online calculator from patient medication lists at the time of cognitive evaluation; Parkinson's Measurement, n.d.), relevant medical comorbidities (e.g., comorbidities indicating vascular risk such as hypertension and hyperlipidemia), and psychiatric comorbidities (i.e., depression, anxiety). The Hoehn & Yahr scale classifies patients with PD based on level of clinical severity observed and ranges from stages I (1; "Unilateral involvement only, usually with minimal or no functional impairment") to V (5; "Confinement to bed or wheelchair unless aided") (Hoehn & Yahr, 1967). The scale was later modified to include ratings 1.5 and 2.5 (Jankovic et al., 1990). Hoehn & Yahr ratings, as opposed to other indicators of PD symptom severity such as Unified Parkinson's Disease

Rating Scale (UPDRS) scores, were included based on their availability in current medical records. Functional ability level (i.e., independent with basic and instrumental activities of daily living, independent with motor difficulty, some assistance with instrumental activities of daily living, major assistance with activities of daily living, dependent) and cognitive diagnosis (i.e., normal cognition, mild changes consistent with PD, mild neurocognitive disorder or MCI, major neurocognitive disorder) at the time of evaluation were also recorded. Test performance on cognitive tests was recorded as standard scores (M = 100, SD = 15) except for raw scores for the Montreal Cognitive Assessment (MoCA out of 30 points; Nasreddine et al., 2005) and affective measures (e.g., Geriatric Depression Scale out of 30 points; Yesavage, 1988).

Patients meeting MDS criteria for PDD (Emre et al., 2007) were excluded from being labeled MCI. Namely, patients for whom functional ability level was rated as 'major assistance with activities of daily living' or 'dependent,' all of whom were diagnosed with major neurocognitive disorder per their neuropsychological reports, were excluded (n = 19). Also excluded were patients for whom the test battery did not include two tests in each of the five cognitive domains per MDS criteria (n = 9).

Following application of exclusion criteria, PD-MCI was identified according to MDS Level I and Level II criteria (Litvan et al., 2012). Cut points for Levels I and II can be found in Table 2.1. PD-MCI was also identified using the same standard deviation rules below each patient's premorbid functioning level to examine whether consideration of a patient's individual premorbid level enhanced sensitivity to MCI for higher functioning patients. Premorbid levels were assessed at the time of the evaluation via combination of word reading, vocabulary, and a demographic-based estimate (Barona, Reynolds, &

Table 2.1 PD-MCI Level I and Level II cut points

	MoCA†	DRS Total Score	1-2 SD Below Norm	1 SD Below Norm	1.5 SD Below Norm	2 SD Below Norm
Level I	21-25[a]	70-85[b]				
Level II			70-85	< 85	< 77	< 70

Note: MoCA = Montreal Cognitive Assessment; DRS = Dementia Rating Scale; SD = standard deviation.
Standard scores except †.
†Raw scores.
[a]Raw score 21 recommended as cutoff for PDD (Dalrymple-Alford et al., 2010).
[b]1-2 standard deviations below population norm (Litvan et al., 2012).

Chastain, 1984). In accordance with MDS criteria, MCI was identified if two or more tests within one domain or two or more tests across multiple domains were below cut points, as defined in Results, regardless of clinician diagnosis by the evaluating neuropsychologist.

2.2 Analyses

Cognitive variables were checked for outliers and significant skewness and kurtosis. Significant left skewness was identified in the Dementia Rating Scale Attention and Construction subscales (skewness < -1), and right skewness in FAS test of phonemic fluency (skewness > 1). Notably, FAS was administered to 18.4% (n = 25) of the total sample, with those exhibiting more significant cognitive deficits (cognitive classifications Mild Neurocognitive Disorder/MCI n = 12 and Major Neurocognitive Disorder n = 11) representing 92% of administrations. Thus, the mean standard score for this measure was in the borderline range (M = 78.16). Another test of phonemic fluency, D-KEFS Letter Fluency, was used more widely and did not exhibit significant skewness. No measures exhibited significant kurtosis (> 3 or < -3). Two potential outliers were identified on FAS and three on Dementia Rating Scale-Construction subscale. As these outliers were within the first interquartile range, they were determined not to represent significant deviations from the mean/median scores and were included in analyses. Bivariate Pearson and point-biserial correlations between demographic factors and cognitive variables were calculated. To examine differences between excluded patients and included patients, ANOVAs were calculated. Cohen's kappa was calculated to examine concordance between clinician diagnostic impression and MCI determination based on Level II criteria. ANOVA and Welch's ANOVA were used to examine performance differences between cognitive

classification groups. Due to the large number of contrasts performed, alpha was set at .01 for all analyses to minimize Type I error rate.

Receiver operating characteristic (ROC) curves were constructed to examine the ability of tests in each of the five cognitive domains to differentiate patients based on MCI classification at 1.5 SD below age and education adjusted norms. ROC curves plot the proportion of patients correctly identified with MCI (sensitivity) against the proportion of those incorrectly identified (1-specificity). Accuracy of the measures is represented in the area under the curve (AUC). Data were analyzed using SPSS version 27.

CHAPTER 3. RESULTS

In total, data from 136 patients were available for inclusion. Demographic characteristics for all patients are presented in Tables 3.1 and 3.2, with clinical characteristics compared by sex via independent samples t tests in Table 3.3. Table 3.4 displays correlations between LEDD, highest frequency medical factors (hypertension and hyperlipidemia), psychiatric factors (depression and anxiety), and select cognitive variables grouped by Level II assessment domains. Bivariate Pearson correlations were calculated for continuous variables (e,g., LEDD), and point-biserial correlations were calculated for the categorical medical and psychiatric factors. Education exhibited significant relationships with most cognitive variables, with the exception of an executive and language measure. LEDD did not demonstrate significant correlations with cognitive variables. In contrast, Hoehn & Yahr off and on scores exhibited multiple significant correlations, the strongest relationship being between Hoehn & Yahr off score and Weschler Abbreviated Scale of Intelligence-II Full Scale IQ (WASI-II FSIQ; r = -.379, p

Table 3.1 Descriptive characteristics (frequencies) for all patients

	Frequency (n = 136)
Handedness	
Right	126 (92.6%)
Missing	1 (0.7%)
Ethnicity	
White	130 (95.6%)
Asian	1 (0.7%)
Latinx	3 (2.2%)
South American	2 (1.5%)
Sex	
Male	81 (59.6%)
Hypertension	73 (53.7%)
Hyperlipidemia	44 (32.4%)
Diabetes Mellitus	26 (19.1%)
CAD	12 (8.8%)
COPD	7 (5.1%)
Stroke/TIA	16 (11.8%)
Myocardial Infarction	1 (0.7%)
Obstructive Sleep Apnea	19 (14.0%)
Headache/Migraine	11 (8.1%)
mTBI	8 (5.9%)
TBI	3 (2.2%)
Cancer	9 (6.6%)
Anemia	7 (5.1%)
Depression	27 (19.9%)
Anxiety	30 (22.1%)

Note: CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack; mTBI = mild traumatic brain injury; TBI = traumatic brain injury.

Table 3.2 Descriptive characteristics (means) for all patients (n = 136)

	Mean (SD)
Age	65.51 (8.60)
Education	14.11 (3.27)
Hoehn & Yahr (off)	2.69 (0.91)
Hoehn & Yahr (on)	2.25 (0.69)
LEDD	608.27 (575.83)

Note: LEDD = levodopa equivalent daily dose.

Table 3.3 Descriptive characteristics (means) for all patients (n = 136) by sex

	Male (n)	Female (n)	Male M (SD)	Female M (SD)	*t* (*p*)
Age	81	55	65.52 (8.54)	65.51 (8.76)	.01 (.995)
Education	78	55	14.14 (3.43)	14.05 (3.05)	.15 (.881)
Hoehn & Yahr (off)	56	40	2.48 (.79)	2.98 (1.00)	-2.70 (.008)*
Hoehn & Yahr (on)	48	39	2.08 (.54)	2.46 (.79)	-2.55 (.013)
LEDD	81	55	617.20 (584.71)	595.13 (567.59)	.22 (.827)

Note: *$p < .01$.
LEDD = levodopa equivalent daily dose.

Table 3.4 Correlations between high frequency demographic factors and select cognitive variables by domain

	Education	Hoehn & Yahr (off)	Hoehn & Yahr (on)	LEDD	Hypertension	Hyperlipidemia	Depression	Anxiety
General								
Premorbid Functioning (WRAT-4 Word Reading)	.689**	-.255	-.178	.011	-.003	.033	-.126	-.132
WASI-II FSIQ	.606**	-.379**	-.338*	-.028	.055	-.046	-.069	-.166
Attention/Working Memory								
WAIS-IV Digit Span	.444**	-.206	-.208	-.019	-.051	-.080	-.020	.002
D-KEFS Trails – Number Sequencing	.367**	-.191	-.133	-.086	.116	.060	.025	-.004
Executive Functioning								
D-KEFS Trails – Switch	.434**	-.343*	-.267	-.146	.007	-.007	.016	-.046
Stroop Color-Word	.158	-.321*	-.321*	-.036	.038	-.128	-.028	-.138
Language								
WASI-II Vocabulary	.568**	-.350*	-.298*	.022	-.015	-.094	-.031	-.162
BNT-2	.232	-.288*	-.125	-.026	.035	.040	-.129	-.148
Memory								
HVLT-R Delay	.249*	.004	-.038	-.032	-.092	-.060	.005	.117
BVMT-R Delay	.292*	-.220	-.224	-.095	.111	-.132	.018	.005
Visuospatial								
WASI-II Block Design	.375**	-.218	-.257	.028	.040	-.143	-.148	-.240
JOLO	.324**	-.342*	-.251	-.028	.006	-.062	-.109	-.096

Note: *$p < .01$; **$p < .001$.

BNT-2 = Boston Naming Test-2nd Edition; BVMT-R = Brief Visuospatial Memory Test-Revised; D-KEFS = Delis-Kaplan Executive Function System; JOLO = Judgment of Line Orientation; LEDD = levodopa equivalent daily dose; FSIQ = Full Scale Intelligence

Table 3.4 (continued)
Quotient; HVLT-R = Hopkins Verbal Learning Test-Revised; WAIS-IV = Wechsler Adult Intelligence Scale 4th Edition; WASI-II = Wechsler Abbreviated Scale of Intelligence-2nd Edition; WRAT-4 = Wide Range Achievement Test 4th Edition.

< .001). A linear regression model further indicated that Hoehn & Yahr off scores were a significant predictor of FSIQ ($F^{(1,81)} = 13.61$, $p < .001$), with 14.4% of the variance in FSIQ scores explained by Hoehn & Yahr off score ($\beta 1 = -5.77$, $p < .001$). This is more variance than Hoehn & Yahr off score explained for FSIQ's composite Verbal Comprehension Index (11.1%) or Perceptual Reasoning Index (9.8%) alone, per additional linear regression analyses. Medical and psychiatric factors did not demonstrate significant relationships with cognitive performance. Hypertension was specifically probed for its demonstrated relationship with executive functioning (Jones et al., 2014), with *t* tests revealing no significant effect of presence of hypertension on Delis-Kaplan Executive Function System (D-KEFS) Trails – Switching [$t(111) = -.075$, $p = .940$] or Stroop Color-Word [$t(108) = -.415$, $p = .679$] performances. Given the prevalence of stroke/TIA in the current sample (11.8%), this factor was further probed. Patients with stroke/TIA were distributed throughout the cognitive classification groups as follows: No diagnosis (n = 0), mild changes consistent with PD (n = 4), mild neurocognitive disorder/MCI (n = 6), major neurocognitive disorder (n = 6). Chi square analysis indicated that distribution in these groups were not significantly different ($r = 5.00$, $p = .172$).

Standard scores on all cognitive measures for all patients are displayed in Table 3.5. Measures with data reported for fewer than 10 patients were not included. These measures are: Averaged premorbid estimate; Peabody Picture Vocabulary Test-4; California Verbal Learning Test-II; Neuropsychological Assessment Battery, Shape Recognition; Conners' Continuous Performance Test-II; Wechsler Memory Scale-III (WMS) Working Memory Index and individual measures (Letter-Number Sequencing, Spatial Span, Digit Span); D-KEFS Color-Word Interference Test; Wisconsin Card Sort

Table 3.5 Performance on cognitive and mood variables for all patients (N = 136)

	n	Raw (SD)	M (SD)	Descriptor
Cognitive Screeners				
DRS-2 Total	85		87.82 (17.16)	Low Average
Attention	82		99.67 (13.53)	Average
Initiation-Perseveration	82		90.30 (15.08)	Average
Construction	82		92.87 (12.20)	Average
Conceptualization	82		91.10 (14.76)	Average
Memory	82		91.04 (16.04)	Average
MoCA	39	23.85 (4.26)		--
Premorbid Functioning				
Premorbid Functioning (WRAT-4 Word Reading)	131		95.41 (14.16)	Average
Barona demographic estimate	31		101.55 (9.16)	Average
General Intellectual Functioning				
WASI-II FSIQ	111		88.50 (15.32)	Low Average
VCI	109		93.01 (13.94)	Average
PRI	109		86.33 (16.01)	Low Average
KBIT-2 IQ	22		87.41 (16.09)	Low Average
Verbal	22		89.86 (14.45)	Low Average
Nonverbal	22		86.14 (19.00)	Low Average
Attention/Working Memory				
WAIS-IV Digit Span	126		93.17 (15.89)	Average
Stroop Word Reading	125		77.33 (15.43)	Borderline
Stroop Color Naming	125		78.80 (16.36)	Borderline
D-KEFS Trails – Motor Speed	116		92.54 (17.91)	Average

Table 3.5 (continued)

D-KEFS Trails – Visual Scanning	115		90.04 (18.66)	Average
D-KEFS Trails – Number Sequencing	115		87.18 (21.93)	Low Average
D-KEFS Trails – Letter Sequencing	115		85.37 (22.65)	Low Average
SDMT Written	96		81.19 (19.94)	Low Average
SDMT Oral	95		82.62 (20.15)	Low Average
TMT Part A	14		78.79 (19.67)	Borderline
Executive Functioning				
Stroop Color-Word	126		87.40 (15.34)	Low Average
D-KEFS Trails – Switching	118		85.10 (23.87)	Low Average
WASI-II Matrix Reasoning	110		86.97 (15.76)	Low Average
D-KEFS Letter Fluency	108		94.50 (19.34)	Average
D-KEFS Category Fluency	108		95.35 (20.36)	Average
D-KEFS Verbal Fluency - Switching	106		89.91 (19.72)	Low Average
Animals	50		83.18 (20.93)	Low Average
FAS	25		78.16 (20.96)	Borderline
KBIT-2 Riddles	18		92.17 (15.06)	Average
KBIT-2 Matrices	17		87.41 (15.12)	Low Average
TMT Part B	14		72.93 (20.47)	Borderline
Language				
WASI-II Vocabulary	110		96.27 (14.99)	Average
WASI-II Similarities	109		90.75 (13.41)	Average
BNT-2	100		89.11 (16.86)	Low Average

Table 3.5 (continued)

BNT-2 30 Item	32		93.00 (19.30)	Average
MAE Token Test	18		96.67 (18.11)	Average
WAIS-IV Vocabulary	18		95.67 (16.71)	Average
KBIT-2 Verbal Knowledge	17		91.76 (14.18)	Average
Memory				
HVLT-R Learning	133		79.80 (17.06)	Borderline
HVLT-R Delay	133		75.21 (20.18)	Borderline
HVLT-R Recognition	133		83.07 (18.92)	Low Average
WMS-IV LMI	132		90.83 (18.13)	Average
WMS-IV LMII	132		88.56 (18.11)	Low Average
BVMT-R Learning	99		75.58 (18.86)	Borderline
BVMT-R Delay	99		80.09 (21.93)	Low Average
NAB Shape Learning - Immediate	22		93.27 (21.05)	Average
NAB Shape Learning – Delay	21		96.00 (17.69)	Average
BVMT-R Copy	18	8.5 (3.62)		--
Visuospatial				
JOLO	132		89.86 (18.60)	Low Average
WASI-II Block Design	107		88.36 (15.29)	Low Average
WAIS-IV Block Design	23		89.22 (16.33)	Low Average
BVFD	10		81.20 (12.73)	Low Average
Mood				
GDS	93	10.31 (6.78)		Mild
GDS-15	16	4.63 (2.94)		Normal/Mild
BAI	15	17.20 (9.92)		Moderate

Note: M = mean, SD = standard deviation; results presented in standard scores (M=100, SD=15) with the exception of raw scores for MoCA (total possible = 30), BVMT-R Copy (total possible = 12), GDS (total possible = 30), GDS-15 (total possible = 15), and BAI (total possible = 63).

BAI = Beck Anxiety Inventory; BNT-2 = Boston Naming Test-2nd Edition; BVFD = Benton Visual Form Discrimination; BVMT-R = Brief Visuospatial Memory Test-Revised; D-KEFS = Delis-Kaplan Executive Function System; DRS-2 = Dementia

Table 3.5 (continued)
Rating Scale 2nd Edition; FAS = F-A-S Phonemic Verbal Fluency Test; FSIQ = Full Scale Intelligence Quotient; GDS = Geriatric Depression Scale; GDS-15 = GDS 15 item version; HVLT-R = Hopkins Verbal Learning Test-Revised; JOLO = Judgment of Line Orientation; KBIT-2 = Kaufman Brief Intelligence Test 2nd Edition; MAE = Multilingual Aphasia Examination; MoCA = Montreal Cognitive Assessment; PRI = Perceptual Reasoning Index; SDMT = Symbol Digit Modalities Test; TMT = Trail Making Test;
Table 3.5 (continued)
VCI = Verbal Comprehension Index; WAIS-IV = Wechsler Adult Intelligence Scale 4th Edition; WASI-II = Wechsler Abbreviated Scale of Intelligence-2nd Edition; WMS-IV LM = Wechsler Memory Scale 4th Edition Logical Memory subtest; WRAT-4 = Wide Range Achievement Test 4th Edition.

Test; and Wechsler Adult Intelligence Scale-IV (WAIS-IV) Similarities and Matrix Reasoning. Mood measures with data for fewer than 10 patients (Beck Depression Inventory-II; Personality Assessment Inventory) are also not displayed. Measures were assigned to cognitive domains according to MDS criteria (Litvan et al., 2012). Table 3.6 displays standard scores for all measures according to cognitive classification, with Table 3.7 comparing standard scores on select cognitive measures by sex. Scores were compared across classification groups using ANOVA and Tukey follow-up contrasts for most measures. The results of Levene's test indicated significant heterogeneity of variances for some dependent variables (indicated on the table). Because of this violation of the assumption of homogeneity of variance, analyses for these variables utilized Welch's ANOVA omnibus tests and Games-Howell follow-up contrasts. Independent sample t tests were utilized for sex comparisons.

Functional status and clinician diagnostic impressions for all patients are presented in Tables 3.8 and 3.9, respectively, with clinical diagnostic impressions by sex displayed in Table 3.10. Regarding functional ability level, 13.2% (n = 18) were rated as requiring 'major assistance with activities of daily living,' and 0.7% (n = 1) were rated as 'dependent.' These patients (n = 19) were excluded from subsequent MCI-related analyses as they met criteria for PDD, leaving 117 patients. Chi square analysis revealed no significant difference in observed frequencies of diagnostic impressions by sex (r = 4.08, p = .253). Table 3.11 displays results of Welch's ANOVAs examining demographic differences between those excluded for lower functional status and the remaining patients. Age, education, and Hoehn & Yahr off scores were significantly lower for those with lower functional status compared to the remaining patients ($p < .01$). Welch's ANOVAs were

Table 3.6 Performance on cognitive and mood variables by cognitive classification

	Normal Cognition (n = 13); M (SD)	Mild Changes Consistent with PD (n = 21); M (SD)	Mild Neurocognitive Disorder/MCI (n = 70); M (SD)	Major Neurocognitive Disorder (n = 32); M (SD)	*F* (*p*)
Cognitive Screeners					
DRS-2 Total	104.29 (9.76)	102.08 (6.89)	91.16 (13.71)	69.13 (11.45)[abc]	29.24 (<.001)**
Attention[#]	110.00 (9.57)	102.92 (6.20)	102.95 (10.21)	89.13 (16.42)[abc]	9.14 (<.001)**
Initiation- Perseveration[#]	104.29 (3.45)	102.08 (7.82)	91.63 (13.22)[a]	77.61 (13.56)[abc]	15.26 (<.001)**
Construction[#]	97.86 (5.67)	93.75 (7.72)	95.00 (11.60)	87.17 (14.83)	2.64 (.055)
Conceptualization[#]	97.14 (6.99)	100.00 (8.79)	95.88 (10.91)	76.30 (14.63)[abc]	17.72 (<.001)**
Memory	102.14 (10.35)	104.58 (9.88)	93.13 (12.74)	76.96 (15.06)[abc]	15.56 (<.001)**
MoCA†	27.4 (1.82)	25.75 (2.60)	24.20 (3.35)	17.17 (3.25)[abc]	12.94 (<.001)**
Premorbid Functioning					
Premorbid Functioning (WRAT-4 Word Reading)	101.92 (15.18)	99.52 (14.35)	96.39 (12.83)	87.53 (13.75)[a]	5.16 (.002)*
Barona demographic estimate	108.80 (5.81)	--	102.83 (8.00)	96.54 (8.60)	4.12 (.016)
General Intellectual Functioning					
WASI-II FSIQ	99.92 (10.02)	97.11 (10.79)	90.33 (13.66)	71.33 (9.56)[abc]	23.88 (<.001)**
VCI	99.69 (9.18)	100.42 (8.43)	95.43 (12.24)	77.43 (12.10)[abc]	19.56 (<.001)**
PRI[#]	100.31 (11.66)	94.74 (11.49)	87.20 (14.58)	69.43 (9.35)[abc]	21.35 (<.001)**
KBIT-2 IQ^	--	104.00 (1.41)	92.83 (11.86)	75.13 (15.92)	6.03 (.009)*
Verbal	--	106.50 (2.12)	93.25 (10.38)	80.63 (16.12)	4.34 (.028)
Nonverbal^	--	106.50 (2.12)	93.08 (15.44)	70.63 (15.21)	7.46 (.004)*

Table 3.6 (continued)

Attention/Working Memory					
WAIS-IV Digit Span	102.31 (8.81)	97.67 (14.15)	96.86 (15.29)	77.79 (10.19)[abc]	16.80 (<.001)**
Stroop Word Reading	90.46 (12.52)	85.67 (13.36)	77.92 (14.51)	64.93 (10.61)[abc]	14.93 (<.001)**
Stroop Color Naming	94.38 (13.51)	88.67 (11.62)	79.69 (14.12)[a]	63.69 (12.52)[abc]	21.62 (<.001)**
D-KEFS Trails – Motor Speed	102.92 (9.64)	102.11 (13.78)	94.75 (15.82)	75.77 (17.07)[abc]	15.12 (<.001)**
D-KEFS Trails – Visual Scanning	102.92 (14.69)	99.17 (12.04)	93.00 (16.16)	70.20 (15.24)[abc]	19.86 (<.001)**
D-KEFS Trails – Number Sequencing	110.83 (9.73)	96.67 (19.93)	89.27 (18.50)[a]	64.00 (14.14)[abc]	24.87 (<.001)**
D-KEFS Trails – Letter Sequencing[#]	112.92 (6.20)	99.78 (14.84)	84.68 (21.01)[ab]	63.40 (11.79)[abc]	27.50 (<.001)**
SDMT Written	104.08 (22.41)	89.06 (11.67)	78.63 (17.32)[a]	62.43 (11.55)[abc]	15.29 (<.001)**
SDMT Oral[#]	102.75 (23.50)	91.25 (10.29)	81.30 (17.68)	60.50 (9.79)[abc]	15.66 (<.001)**
TMT Part A^	--	--	82.38 (24.13)	70.60 (9.61)	0.73 (.505)
Executive Functioning					
Stroop Color-Word	101.23 (14.25)	94.32 (16.70)	89.46 (12.11)	73.19 (9.88)[abc]	20.71 (<.001)**
D-KEFS Trails – Switching[#]	106.54 (12.14)	100.05 (17.00)	86.68 (22.45)[a]	59.81 (10.91)[abc]	25.86 <.001)**
WASI-II Matrix Reasoning[#]	98.83 (8.28)	93.53 (14.13)	88.35 (15.85)	72.71 (8.50)[abc]	13.52 (<.001)**
D-KEFS Letter Fluency	111.15 (19.38)	96.89 (14.77)	95.53 (18.80)	77.63 (12.06)[abc]	10.32 (<.001)**
D-KEFS Category Fluency	108.85 (20.33)	106.89 (17.70)	94.30 (18.36)	77.68 (14.93)[abc]	11.28 (<.001)**

Table 3.6 (continued)

D-KEFS Verbal Fluency - Switching	103.08 (14.65)	101.39 (15.42)	89.11 (18.81)	72.37 (15.40)[abc]	11.78 (<.001)**
Animals	115.00 (25.46)	112.67 (19.62)	81.46 (12.94)[b]	70.94 (18.23)[ab]	12.69 (<.001)**
FAS^	--	114.50 (34.65)	82.92 (17.03)	66.36 (13.06)	8.02 (.002)*
KBIT-2 Riddles	--	113.00 (18.38)	93.73 (13.33)	80.40 (6.15)	5.25 (.019)
KBIT-2 Matrices^	--	102.50 (3.54)	92.20 (12.78)	71.80 (8.23)	7.60 (.006)*
TMT Part B	--	--	80.50 (21.81)	62.20 (16.10)	1.36 (0.296)
Language					
WASI-II Vocabulary	105.25 (14.46)	101.74 (12.50)	98.42 (13.11)	82.54 (12.82)[abc]	12.27 (<.001)**
WASI-II Similarities[#]	94.08 (6.04)	99.42 (6.95)	93.38 (11.98)	75.57 (11.98)[abc]	20.82 (<.001)**
BNT-2	93.20 (8.88)	98.56 (17.15)	89.49 (15.25)	77.89 (18.92)[b]	5.30 (.002)*
BNT-2 30 Item[#]	108.00 (3.46)	101.80 (15.16)	98.77 (11.00)	78.09 (22.82)[a]	4.84 (.008)*
MAE Token Test[#]	--	114.00 (0.00)	98.73 (13.60)	85.20 (24.61)	2.29 (.135)
WAIS-IV Vocabulary	--	125.00 (14.14)	93.20 (12.34)	90.00 (15.49)	5.35 (.018)
KBIT-2 Verbal Knowledge^	--	113.00 (2.83)	93.30 (11.76)	80.20 (9.63)	6.88 (.008)*
Memory					
HVLT-R Learning[#]	97.17 (8.60)	87.65 (16.43)	79.76 (17.01)[a]	68.10 (10.69)[abc]	13.34 (<.001)**

Table 3.6 (continued)

HVLT-R Delay[#]	104.33 (10.95)	89.20 (17.58)	71.73 (18.45)[ab]	62.77 (10.56)[ab]	24.94 (<.001)**
HVLT-R Recognition	102.83 (10.61)	95.15 (16.19)	83.01 (17.74)[a]	67.74 (12.13)[abc]	19.80 (<.001)**
WMS-IV LMI	109.62 (17.01)	98.33 (15.28)	90.35 (16.56)[a]	78.53 (14.66)[abc]	13.45 (<.001)**
WMS-IV LMII	106.92 (12.17)	97.43 (13.24)	88.07 (16.48)[a]	75.50 (16.94)[abc]	14.99 (<.001)**
BVMT-R Learning[#]	102.45 (11.99)	87.08 (18.00)	73.16 (16.04)[a]	62.17 (10.18)[abc]	21.98 (<.001)**
BVMT-R Delay[#]	109.27 (13.86)	95.15 (23.19)	77.92 (17.82)[a]	63.17 (12.26)[abc]	22.21 (<.001)**
NAB Shape Learning – Immediate	--	107.50 (12.55)	91.08 (21.96)	71.33 (15.04)	2.53 (.089)
NAB Shape Learning – Delay	--	102.50 (10.46)	92.36 (19.71)	93.00 (25.51)	.520 (.674)
BVMT-R Copy†[#]	--	--	9.56 (1.88)	6.88 (4.64)	1.82 (.196)
Visuospatial					
JOLO	104.15 (11.58)	97.90 (14.09)	92.41 (17.16)	71.59 (14.11)[abc]	19.36 (<.001)**
WASI-II Block Design[#]	98.33 (11.05)	97.21 (10.17)	89.51 (14.91)	73.22 (9.52)[abc]	16.45 (<.001)**
WAIS-IV Block Design	--	110.00 (7.07)	91.14 (16.50)	79.43 (10.75)	3.71 (.043)

Table 3.6 (continued)

BVFD	--	86.50 (2.12)	83.60 (11.97)	73.67 (17.67)	.743 (.510)
Mood					
GDS†[#]	11.44 (10.93)	7.14 (5.61)	9.64 (5.84)	13.70 (6.42)	3.14 (.029)
GDS-15†	--	3.00 (2.71)	4.25 (3.30)	5.63 (2.83)	1.12 (.355)
BAI†	--	10.50 (2.12)	18.67 (10.22)	18.67 (14.22)	.392 (.761)

Note: M = mean, SD = standard deviation; results presented in standard scores (M=100, SD=15) with the exception of †.
†Raw scores.
--Measure comprised of 0 or 1 data points for the group.
*$p < .01$.
**$p < .001$.
[a]Statistically significantly different ($p < .01$) from Normal Cognition.
[b]Statistically significantly different ($p < .01$) from Mild Changes Consistent with PD.
[c]Statistically significantly different ($p < .01$) from Mild Neurocognitive Disorder/MCI.
^Post-hoc comparison not performed despite significant group differences due to limited sample size on a measure in one or more classification groups.
[#]Welch's ANOVA and Games-Howell follow-up contrasts (where indicated by significant ANOVA).
BAI = Beck Anxiety Inventory; BNT-2 = Boston Naming Test 2nd Edition; BVFD = Benton Visual Form Discrimination; BVMT-R = Brief Visuospatial Memory Test-Revised; D-KEFS = Delis-Kaplan Executive Function System; DRS-2 = Dementia Rating Scale 2nd Edition; FAS = F-A-S Phonemic Verbal Fluency Test; FSIQ = Full Scale Intelligence Quotient; GDS = Geriatric Depression Scale; GDS-15 = GDS 15 item version; HVLT-R = Hopkins Verbal Learning Test-Revised; JOLO = Judgment of Line Orientation; KBIT-2 = Kaufman Brief Intelligence Test 2nd Edition; MAE = Multilingual Aphasia Examination; MoCA = Montreal Cognitive Assessment; PRI = Perceptual Reasoning Index; SDMT = Symbol Digit Modalities Test; TMT = Trail Making Test; VCI = Verbal Comprehension Index; WAIS-IV = Wechsler Adult Intelligence Scale 4th Edition; WASI-II = Wechsler Abbreviated Scale of Intelligence-2nd Edition; WMS-IV LM = Wechsler Memory Scale 4th Edition Logical Memory subtest; WRAT-4 = Wide Range Achievement Test 4th Edition.

Table 3.7 Performance on select cognitive variables by sex (N = 110)

	Male (n)	Female (n)	Male M (SD)	Female M (SD)	*t* (*p*)
Attention/Working Memory					
WAIS-IV Digit Span	62	42	94.77 (16.71)	97.31 (13.25)	-.82 (.412)
D-KEFS Trails – Number Sequencing	59	37	87.05 (19.50)	98.24 (19.48)	-2.74 (.007)*
Executive Functioning					
D-KEFS Trails – Switch	59	38	84.24 (21.23)	97.42 (22.44)	-2.92 (.004)*
Stroop Color-Word	62	40	87.37 (14.40)	93.25 (15.14)	-1.97 (.051)
Language					
WASI-II Vocabulary	58	36	96.98 (14.54)	101.69 (13.94)	-1.55 (.124)
BNT-2	50	34	91.66 (16.68)	90.09 (15.15)	.44 (.661)
Memory					
HVLT-R Delay	65	44	70.54 (17.96)	88.07 (19.99)	-4.78 (<.001)**
BVMT-R Delay	53	29	82.36 (20.91)	84.72 (23.17)	-.47 (.639)
Visuospatial					
WASI-II Block Design	58	36	90.38 (14.57)	91.28 (14.37)	-.29 (.771)
JOLO	66	43	92.76 (18.56)	92.56 (16.15)	.06 (.954)
Verbal Fluency					
D-KEFS Letter Fluency	58	36	92.34 (16.59)	102.78 (17.34)	-2.74 (.007)*
D-KEFS Category Fluency	58	36	91.31 (17.34)	105.83 (21.30)	-3.61 (<.001)**

Note: M = mean, SD = standard deviation.
*$p < .01$; **$p < .001$.
BNT-2 = Boston Naming Test-2nd Edition; BVMT-R = Brief Visuospatial Memory Test-Revised; D-KEFS = Delis-Kaplan Executive Function System; JOLO = Judgment of Line Orientation; LEDD = levodopa equivalent daily dose; FSIQ = Full Scale Intelligence Quotient; HVLT-R = Hopkins Verbal Learning Test-Revised; WAIS-IV = Wechsler Adult Intelligence Scale 4th Edition; WASI-II = Wechsler Abbreviated Scale of Intelligence-2nd Edition; WRAT-4 = Wide Range Achievement Test 4th Edition.

Table 3.8 Functional status for all patients (n = 136)

	Frequency
Independent	43 (31.6%)
Independent with Motor Difficulty	33 (24.3%)
Some Assistance (IADLs)	41 (30.1%)
Major Assistance (ADLs)	18 (13.2%)
Dependent	1 (0.7%)

Note: IADL = Instrumental activities of daily living; ADL = activities of daily living.

Table 3.9 Clinician diagnostic impressions for all patients (n = 136)

	Frequency
Normal Cognition	13 (9.6%)
Mild Changes Consistent with PD	21 (15.4%)
Mild Neurocognitive Disorder/MCI	70 (51.5%)
Major Neurocognitive Disorder	32 (23.5%)

Note: MCI = mild cognitive impairment.

Table 3.10 Clinician diagnostic impression frequency for all patients (n = 136) by sex

	Male (n = 81)	Female (n = 55)
Normal Cognition (n = 13)	5	8
Mild Changes Consistent with PD (n = 21)	11	10
Mild Neurocognitive Disorder/MCI (n = 70)	43	27
Major Neurocognitive Disorder (n = 32)	22	10

Note: MCI = mild cognitive impairment.

Table 3.11 Demographic differences between those with worse functional status (Major Assistance, n = 18; Dependent, n=1) and rest of sample (n = 117)

	Worse Functional Status M (SD)	Rest of Sample M (SD)	*F* (*p*)
Age	70.84 (6.19)	64.65 (8.64)	8.98 (.003)*
Education	11.63 (3.22)	14.52 (3.10)	13.96 (<.001)*
Hoehn & Yahr (off)	3.56 (1.24)	2.60 (0.83)	9.89 (.002)*
Hoehn & Yahr (on)	2.83 (0.98)	2.21 (0.65)	4.82 (.031)
LEDD	533.74 (584.09)	620.38 (576.10)	0.37 (.545)

*p<.01.
Note: LEDD = levodopa equivalent daily dose.

selected to account for unequal sample sizes in these comparisons.

For Level II classification, 5.98% (n = 7) of the remaining patients were excluded due to test batteries including less than two tests in each of five cognitive domains. Accordingly, 110 patients were available for inclusion in Level II analyses. Table 3.12 displays results of Welch's ANOVAs examining demographic differences between those excluded for incomplete Level II batteries and the remaining patients. No significant differences were found. Welch's ANOVAs were selected to account for unequal sample sizes in these comparisons.

Frequencies of MCI per Level I and Level II criteria are displayed in Figure 3.1. All SD cut points for MCI, based on both standard deviation from norms as well as from individual premorbid estimates, are displayed. Frequency of MCI per Level I criteria was 20.5%. Use of various cut points per Level II criteria resulted in MCI frequencies ranging from 33.6% (1-2 SD below norms; 1-2 SD below premorbid estimate) to 87.3% (1 SD below norms).

Concordance (Cohen's kappa values) between clinician diagnostic impression and Level II MCI determination can be found in Table 3.13. Of patients with Mild Neurocognitive Disorder/MCI as their clinician diagnostic impression (n = 67), 92.5% (n = 62) met MCI criteria using both SD below norms and SD below premorbid estimate. For 6% (n = 4), criteria was met for cut points below norms only; for 1.5% (n = 1), criteria was met for cut points below premorbid estimate only. The cut point 1.5 SD below norms, at which 73.6% (n = 81) of patients met criteria for MCI, demonstrated the greatest concordance with diagnostic impressions ($\kappa = 0.513$). Given this concordance and the

Table 3.12 Demographic differences between those with incomplete Level II assessment batteries (n = 7) and rest of sample (n = 110)

	Incomplete Level II Batteries M (SD)	Rest of Sample M (SD)	*F* (*p*)
Age	65.14 (8.63)	64.62 (8.68)	0.02 (.877)
Education	14.00 (5.37)	14.55 (2.97)	0.18 (.676)
Hoehn & Yahr (off)	3.00 (1.41)	2.58 (0.80)	0.99 (.322)
Hoehn & Yahr (on)	2.80 (1.64)	2.17 (0.53)	4.64 (.034)
LEDD	678.86 (695.15)	616.65 (571.29)	0.08 (.783)

Note: LEDD = levodopa equivalent daily dose.

Figure 3.1 Frequency of Level I (n = 117) and Level II (n = 110) MCI

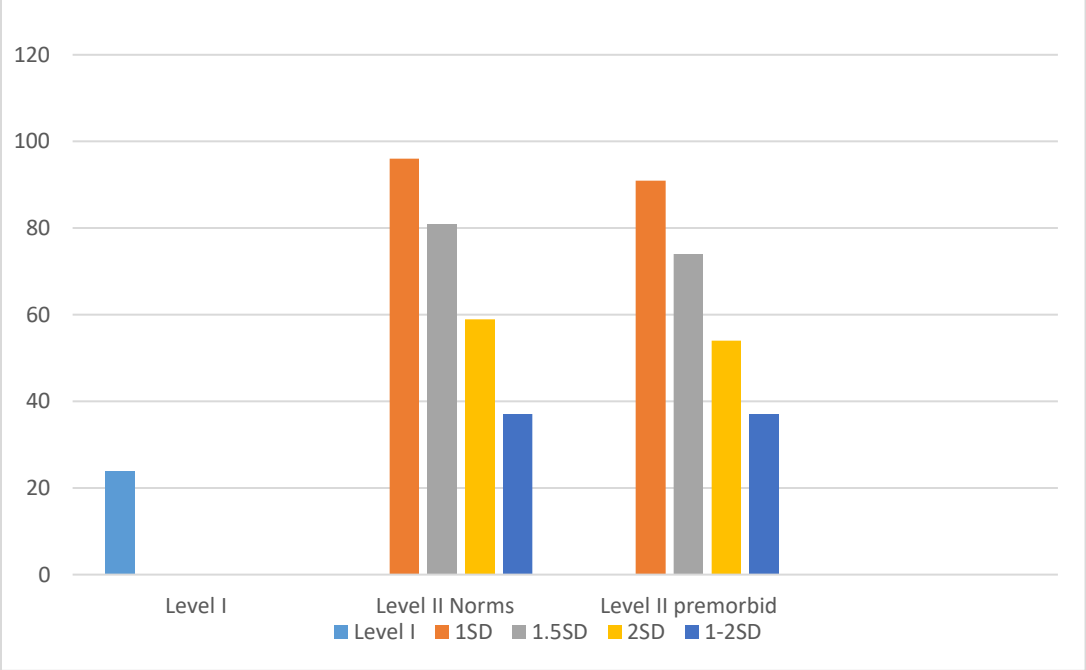


Table 3.13 Cohen's kappa values comparing clinician diagnostic impression and Level II MCI classification

	Level I	*Level II Below Norms*					*Level II Below Premorbid Estimate*			
		1 SD	1.5 SD	2 SD	1-2 SD		1 SD	1.5 SD	2 SD	1-2 SD
Diagnostic Impression MCI	.160	.327	**.513**	.372	-.086		.321	.272	.257	.016

Note: MCI = mild cognitive impairment.

frequent use of this cut point in the PD-MCI literature (Marras et al., 2013; Pfeiffer et al., 2014; Reginold et al., 2013), 1.5 SD below adjusted populations means was subsequently employed in MCI analyses.

Prevalence of single vs. multiple domain impairment for those meeting Level II criteria for MCI at 1.5 SD below norms was 9.1% (n = 10) vs. 64.5% (n = 71), respectively. The remaining 26.4% (n = 29) of those with MCI did not meet criteria at this cut point. Of the five cognitive domains, the memory domain was most often impaired for those with MCI at 1.5 SD below norms (65.5%; n = 72). When limited to MCI – multiple domain, patients' profiles most often included Attention/Working Memory impairment (90.1%; n = 64), followed by Memory impairment (88.7%; n = 63). Of those with MCI – single domain, 90% (n = 9) exhibited memory domain impairment. Of those with MCI – multiple domain, 88.7% (n = 63) exhibited impairment in the memory domain. The language domain was least often impaired (20.9%; n = 23) across single and multiple domain MCI. Frequency of impairment on all domains in Level II MCI can be found in Table 3.14, with Figure 3.2 displaying frequency of affected domains within MCI – multiple domain only.

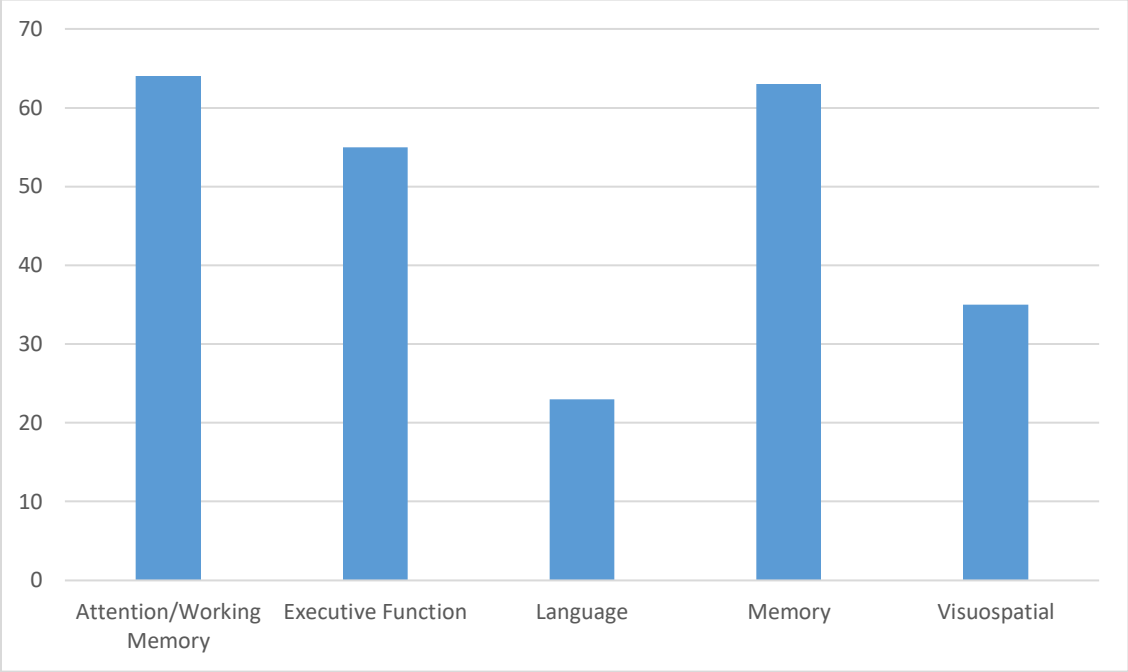
Select cognitive measures were identified for ROC curve construction. In each of the five cognitive domains specified in PD-MCI criteria, the two measures with the largest sample sizes were selected. The following exceptions were made: D-KEFS Trails – Number Sequencing was selected to approximate the Trail Making Test Part A listed in PD-MCI criteria; WASI-II Similarities was not selected for Language given its strong executive component (Higginson et al., 2003); and Brief Visuospatial Memory Test-Revised (BVMT-R) rather than WMS-IV Logical Memory was selected with Hopkins Verbal Learning Test-Revised (HVLT-R) Delay for Memory as to include both verbal and

Table 3.14 Frequency of impairment across cognitive domains in Level II MCI (n = 110)

	Attention/Working Memory	Executive Function	Language	Memory	Visuospatial
Impaired at 1.5 SD below norms (%)	64 (58.2)	55 (50)	23 (20.9)	72 (65.5)	36 (32.7)

Note: MCI = mild cognitive impairment; SD = standard deviations.

Figure 3.2 Frequency of affected domains in MCI – multiple domain at 1.5 SD below norms (n = 71)



Note: MCI = mild cognitive impairment; SD = standard deviations.

non-verbal memory measures. Given the sample sizes displayed in Table 3.5, selected measures were: WAIS-IV Digit Span and Stroop Word Reading (Attention/Working Memory); D-KEFS Trails – Switching and WASI-II Matrix Reasoning (Executive Function); WASI-II Vocabulary and Boston Naming Test-2 (Language); HVLT-R Delay and BVMT-R Delay (Memory); Judgment of Line Orientation and WASI-II Block Design (Visuospatial). ROC curves for two tests in each of the five cognitive domains are presented in Figure 3.3: 3.3A displays Attention/Working Memory measures; 3.3B Executive Function; 3.3C Language; 3.3D Memory; and 3.3E Visuospatial. In order of discrimination ability robustness, Memory measures exhibited excellent discrimination ability (HVLT-R Delay AUC = .779; BVMT-R Delay AUC = .883) when comparing MCI at 1.5 SD below norms to normal cognition at that cut point. Executive function measures demonstrated good to excellent discrimination ability (Stroop Color-Word AUC = .751; D-KEFS Trails Switch AUC = .829). Visuospatial measures demonstrated good discrimination ability (WASI-II Block Design AUC = 0.771; Judgment of Line Orientation AUC = .728). Attention/Working Memory measures exhibited fair to excellent discrimination ability (WAIS-IV Digit Span AUC = .662; D-KEFS Trails Number Sequencing AUC = .795). Language measures exhibited fair discrimination ability (WASI-II Vocabulary AUC = .696; Boston Naming Test-2 AUC = .695).

From these ROC curves, cut scores optimizing sensitivity and specificity for MCI were identified. Overall, memory measures (i.e., HVLT-R Delay and BVMT-R Delay) exhibited notably robust sensitivity and specificity for MCI. The BVMT-R demonstrated the highest sensitivity with excellent specificity. An executive function measure, D-KEFS Trails Switching, demonstrated the highest specificity but with fair sensitivity. From these

Figure 3.3 ROC curves differentiating between MCI at 1.5 SD below norms and normal cognition

Note: Curves display the differentiating ability of:

A) Attention/Working Memory measures (WAIS-IV Digit Span and D-KEFS Trails Number Sequencing, respectively);

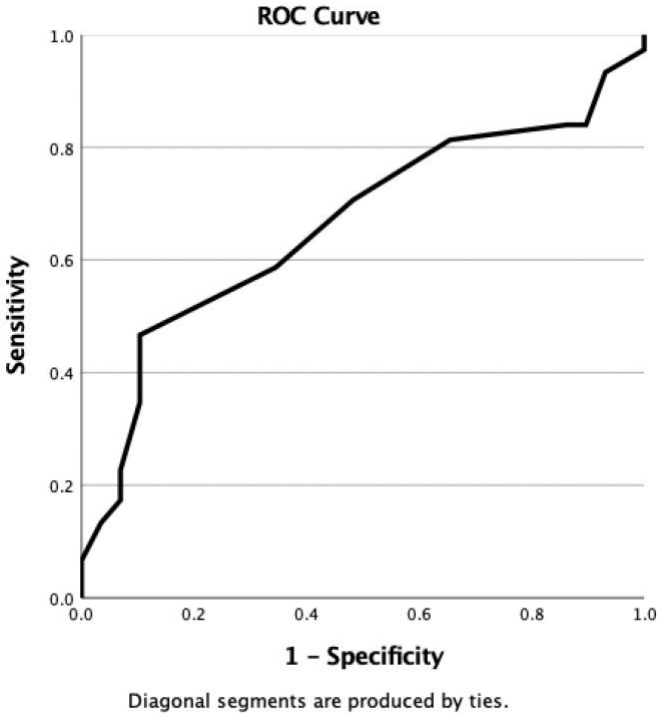
B) Executive Function (D-KEFS Trails Switching and Stroop Color-Word, respectively);

C) Language (WASI-II Vocabulary and Boston Naming Test-2, respectively);

D) Memory (HVLT-R Delay and BVMT-R Delay, respectively);

E) Visuospatial (WASI-II Block Design and Judgment of Line Orientation, respectively)

Figure 3.3A Attention/Working Memory (WAIS-IV Digit Span; D-KEFS Trails Number Sequencing)



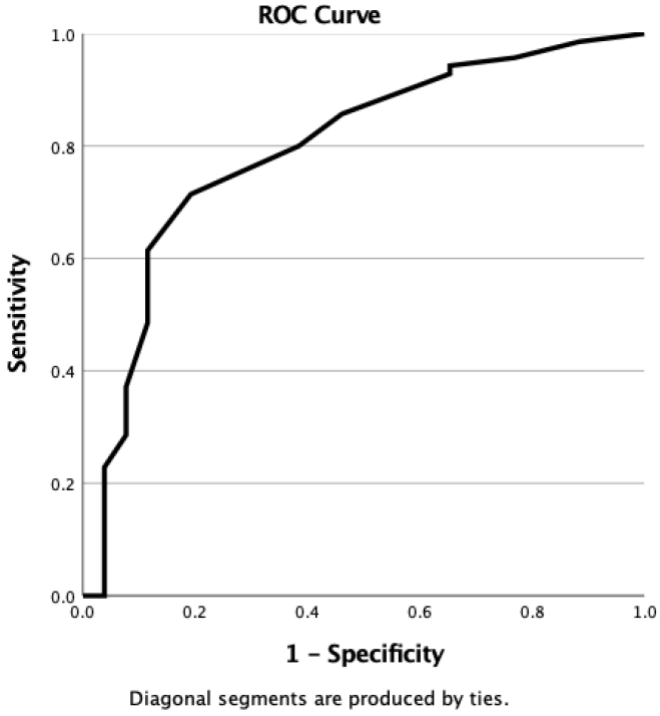
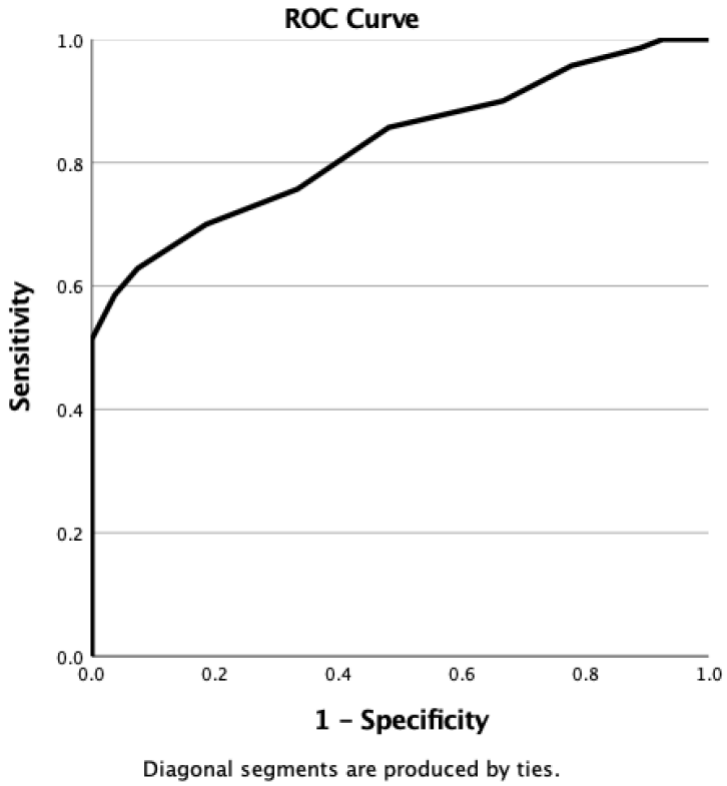


Figure 3.3B Executive Function (D-KEFS Trails Switching; Stroop Color-Word)



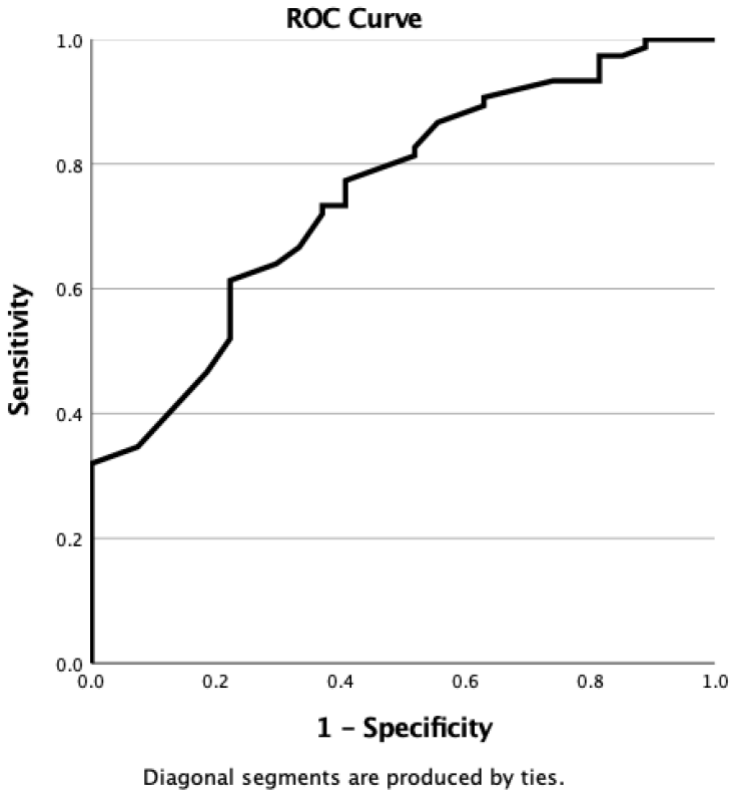
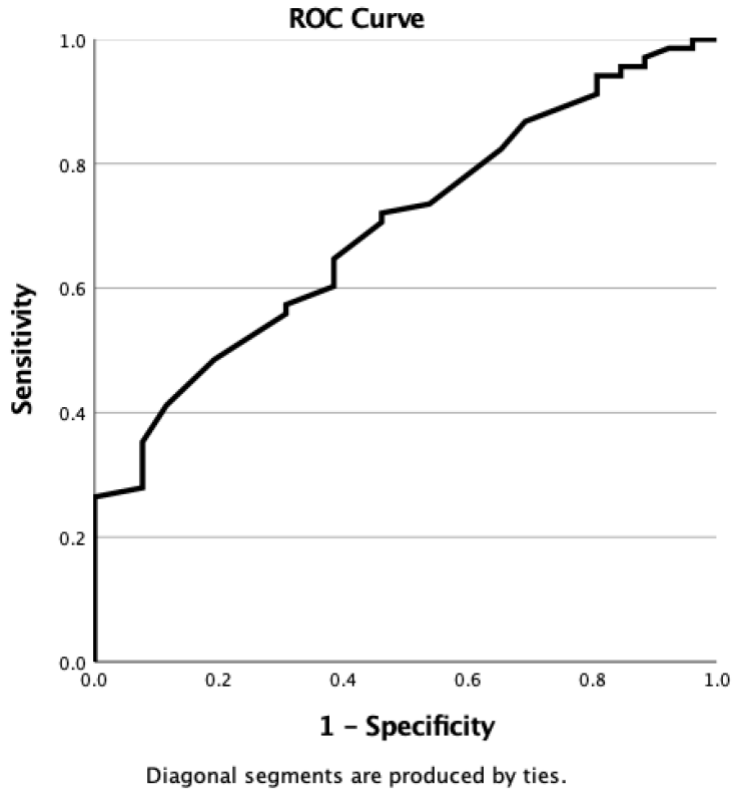


Figure 3.3C Language (WASI-II Vocabulary; Boston Naming Test-2)



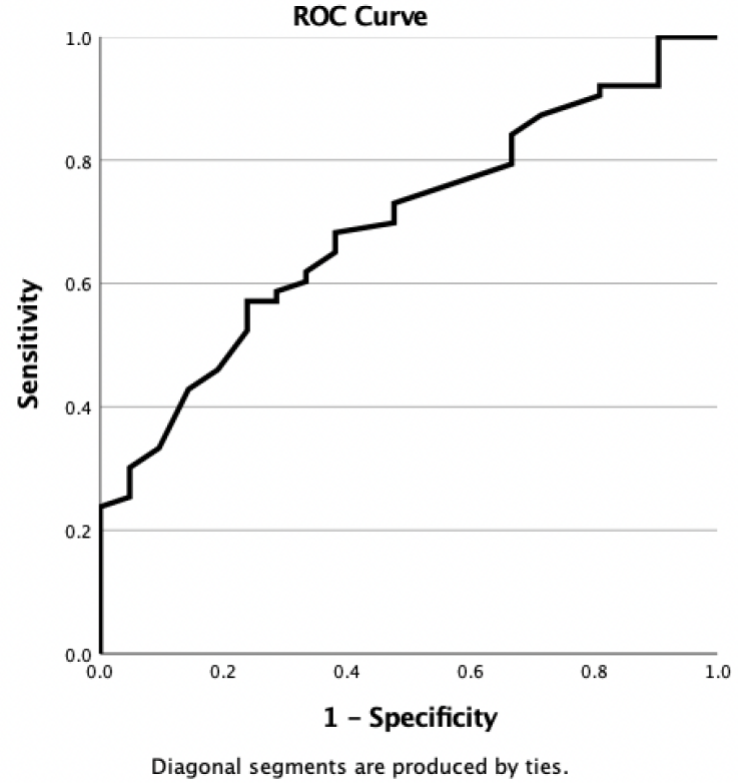
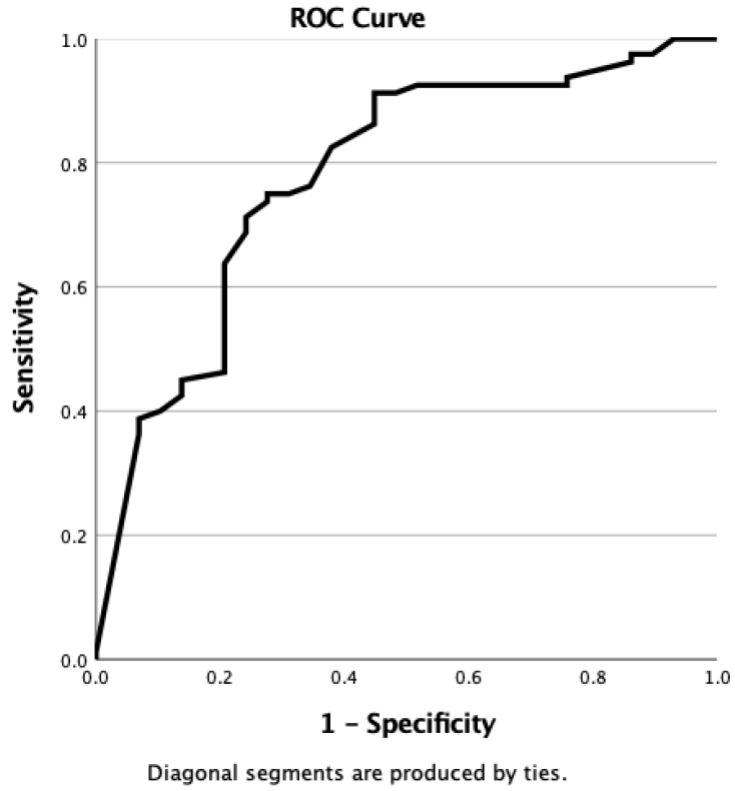


Figure 3.3D Memory (HVLT-R Delay; BVMT-R Delay)



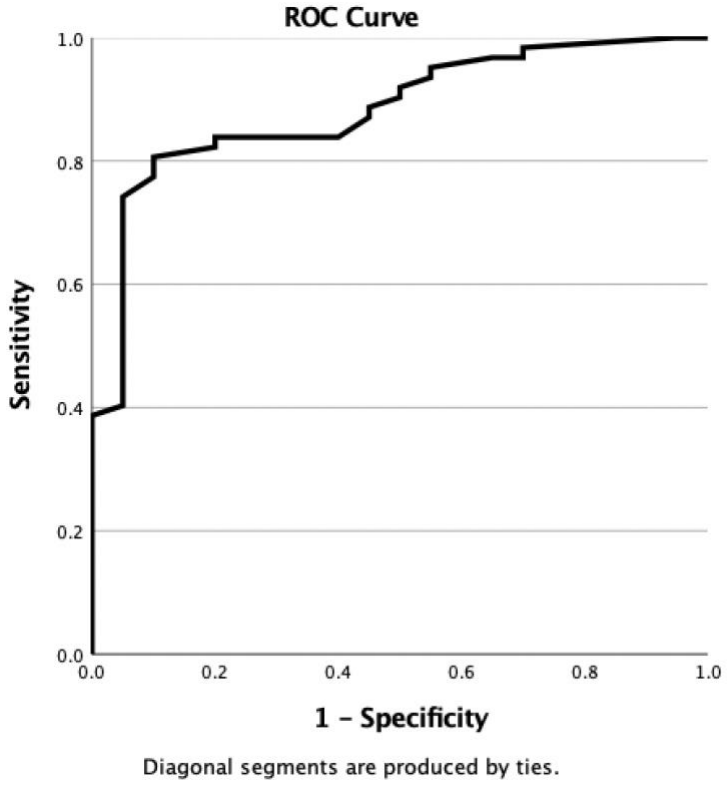
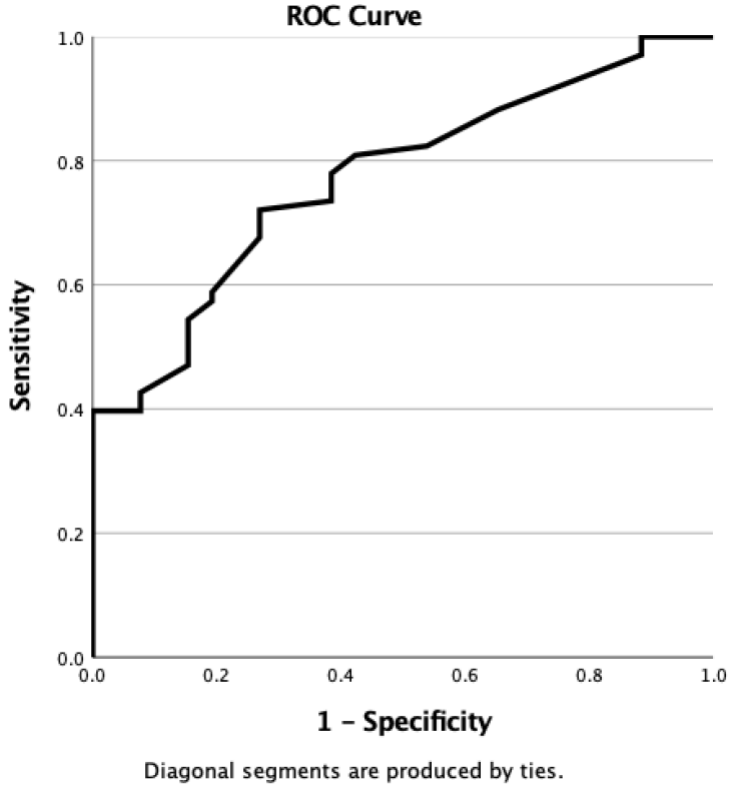
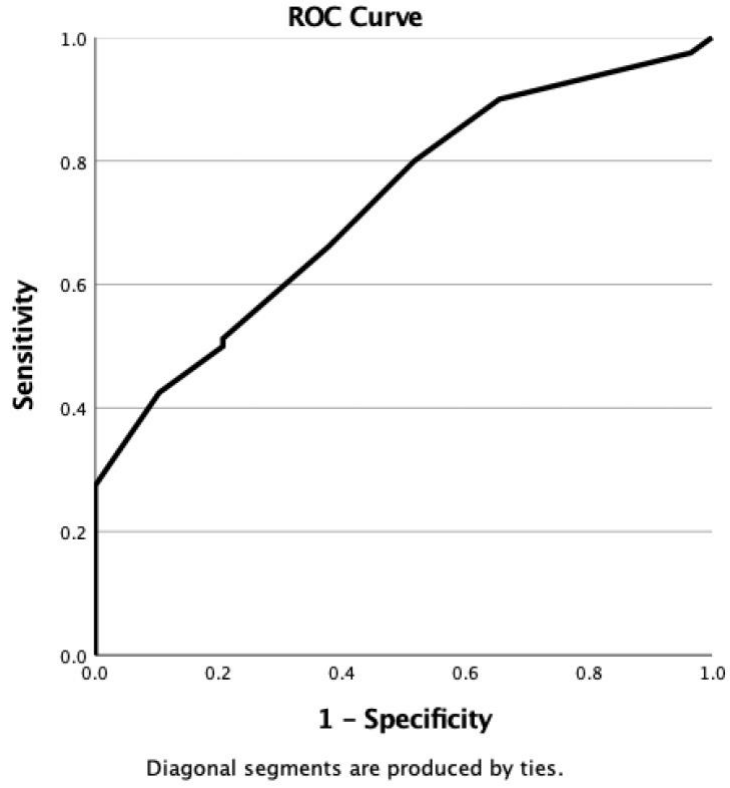


Figure 3.3E Visuospatial (WASI-II Block Design; Judgment of Line Orientation)





sensitivity and specificity values and using the base rate established in the current sample of 73.6% MCI at 1.5 SD below norms, positive and negative predictive values were also calculated. The BVMT-R again demonstrated the most favorable positive and negative predictive values. Recommended cutoffs, sensitivity, specificity, and predictive values are provided in Table 4.1.

CHAPTER 4. DISCUSSION

The present study provides a retrospective cognitive characterization of a cohort of 136 patients with PD seeking DBS from 2017-2020. Prevalence of MCI using Level I criteria was 20.5%, and 73.6% using Level II criteria at the cut point of 1.5 SD below norms. Level II prevalence in the current sample (73.6%) was expectedly higher than prevalence using the less sensitive 2 SD cut point (63.2%; Goldman et al., 2015). Verbal and visual memory measures were most often impaired for those with MCI and demonstrated favorable operating characteristics in differentiating normal cognition from MCI.

Although previously believed to be spared in PD, verbal and visual memory have been increasingly noted as suppressed in PD-MCI. Memory domain impairment is commonly reported in multiple domain MCI, along with deficits in the executive function domain (Foo et al., 2017). Further, amnestic MCI may pose a greater risk for conversion to PDD compared to other MCI subtypes (Cammisuli, Cammisuli, Fusi, Franzoni, & Pruneti, 2019). Impairment in delay recall in particular suggests involvement of other brain regions outside of the fronto-striatal/executive circuit, foreshadowing the involvement of additional subcortical and cortical areas as cognition worsens (Williams-Gray et al., 2007).

Table 4.1 Cut scores optimizing sensitivity and specificity of select cognitive measures

	Cut Score	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Attention/Working Memory					
WAIS-IV Digit Span	≤92.5	.467	.897	.927	.376
D-KEFS Trails – Number Sequencing	≤97.5	.714	.808	.912	.503
Executive Functioning					
D-KEFS Trails – Switch	≤92.5	.629	.926	.960	.472
Stroop Color-Word	≤89	.613	.222	.885	.419
Language					
WASI-II Vocabulary	≤101	.647	.385	.746	.281
BNT-2	≤87.5	.571	.762	.870	.389
Memory					
HVLT-R Delay	≤83	.750	.724	.883	.509
BVMT-R Delay	≤88.5	.806	.900	.957	.625
Visuospatial					
WASI-II Block Design	≤96.5	.721	.731	.882	.485
JOLO	≤99	.663	.621	.830	.398

Note: BNT-2 = Boston Naming Test-2nd Edition; BVMT-R = Brief Visuospatial Memory Test-Revised; D-KEFS = Delis-Kaplan Executive Function System; JOLO = Judgment of Line Orientation; HVLT-R = Hopkins Verbal Learning Test-Revised; WAIS-IV = Wechsler Adult Intelligence Scale 4th Edition; WASI-II = Wechsler Abbreviated Scale of Intelligence-2nd Edition; WRAT-4 = Wide Range Achievement Test 4th Edition.

Given the relative frequency of reported memory deficits in the literature and the predominance of these deficits in the current sample, impairment in the memory domain may be a strong indicator of cognitive dysfunction in PD and may have driven PD-MCI diagnoses in the current sample.

Analysis of demographic characteristics demonstrated significantly higher Hoehn & Yahr off scores for women than men, suggesting greater disease severity in women in contrast to the established association between male sex and greater disease severity (Meoni, Macerollo, & Moro, 2020). It is possible that women in this sample presented with longer disease duration, information that was not consistently available in medical records and thus was not included in the current analyses. In examining demographic characteristics and their relationship to cognitive performance, indicators of PD disease severity demonstrated weak but significant relationships with various cognitive measures. Specifically, significant correlations were found between Hoehn & Yahr on and off scores and multiple cognitive variables, with the strongest correlation between Hoehn & Yahr off score and a composite measure of general intellectual functioning. Linear regression indicated 14.4% of FSIQ score variance was explained by Hoehn & Yahr off score, with more variance explained for FSIQ than its composite verbal and perceptual reasoning indexes alone. These relationships highlight that higher PD severity based on Hoehn & Yahr scores is associated with worse cognitive function and progression to dementia (Marinus, Zhu, Marras, Aarsland, & van Hilten, 2018). Further, PD-MCI is significantly associated with higher Hoehn & Yahr scores and LEDD, more severe motor symptoms based on UPDRS score, and longer disease duration (Baiano et al., 2020). These

associations could be probed further with the inclusion of presurgical DaTscan imaging for those meeting PD-MCI criteria.

The lack of associations between hypertension or hyperlipidemia and cognitive performance was surprising given the prominence of vascular comorbidities in PD (García et al., 2017) and their documented relationship with cognition, especially attention and executive function (Pilotto et al., 2016). The lack of findings for these vascular comorbidities could be due to the lack of sensitivity of their measurement in the current study (presence or absence of hypertension or hyperlipidemia in their medical record). Consideration of more specific indicators of vascular health, such as white matter hyperintensities or basal ganglia perivascular space on imaging (Park et al., 2019), may be informative.

The lack of significant correlation between depression/anxiety and cognitive performance was also surprising, as depression and anxiety occur relatively frequently in PD, are associated with greater PD severity (Shulman, Taback, Bean, & Weiner, 2001), and affect cognition in PD (Menza, Marin, Kaufman, Mark, & Lauritano, 2004). However, rates of depression and anxiety were lower in the current sample (19.9% and 22%, respectively) than in previous estimates of PD patients (36% and 33%, respectively; Shulman et al., 2001). Depression and anxiety rates may be lower in the current sample due to patients' candidacy for an efficacious treatment for their symptoms, as opposed to rates in patient groups not seeking DBS.

Across cognitive domains, standard scores for all patients were in the borderline to average range with general intellectual functioning as measured by WASI-II FSIQ in the low average (standard score = 88.5) range. This score is lower than expected based on

demographic estimates utilizing the overall mean level of education (14.11 years) in the current sample. This result is likely in part due to 23.5% of the total sample meeting criteria for PDD. When the sample was divided into cognitive classifications and scores examined, those with Major Neurocognitive Disorder produced significantly lower scores than those with normal cognition, mild changes consistent with PD, and MCI across most measures with few exceptions (e.g., Boston Naming Test-2).

Notably, those with MCI produced scores that significantly differed from normal cognition and/or mild changes groups on measures including: one cognitive screener composite score; color naming, number sequencing, letter sequencing, and written coding (Attention/Working Memory); trail making switching and animal naming (Executive Function); verbal list learning, delayed recall, and recognition, story learning and delay, and visual learning and delayed recall (Memory). No statistically significant mean score differences were evident between these groups in Language or Visuospatial domains. The lack of differences in the Language domain was unsurprising given the relative sparing of language abilities in PD without dementia (Goldman & Litvan, 2011). The lack of differences in the Visuospatial domain may be due to visuospatial, particularly visuoperceptual, deficits appearing early in the disease (Cronin-Golomb & Braun, 1997) with significant worsening reserved for the dementia state, although other investigations have found prominent visuospatial deficits in MCI vs. normal cognition (Goldman et al., 2013). The greater number of differences in the Attention/Working Memory, EF, and Memory domains were unsurprising given the documented prominence of these domains in worsening PD cognition (Goldman et al., 2013; Muslimović, Schmand, Speelman, & De Haan, 2007).

When cognitive performances on select measures were analyzed by sex, significant differences were apparent on measures of Attention/Working Memory, EF, Memory, and Verbal Fluency, with men demonstrating lower standard scores than women. These results align with aforementioned differences in these domains between cognitive classifications, as well as previous findings demonstrating male sex as a primary risk factor for poorer cognitive performance (Cholerton et al., 2018). Further, semantic verbal fluency has been identified as a significant predictor of MCI progression in PD (Cholerton et al., 2018), with current results suggesting that such an association may be limited to men given intact semantic verbal fluency in women. Notably, within the Memory domain, differences by sex were limited to verbal memory with similar performances on a measure of visual memory, indicating suppressed visual recall abilities for those with PD regardless of sex.

Overall MCI prevalence according to Level I assessment in the current sample (20.5%) was somewhat lower than established estimates but still generally consistent (26.7%, Litvan et al., 2011; 23%, Merola et al., 2014), and even higher than some Level I estimates (16%, Lawson et al., 2017). Regarding Level II assessment, the prevalence of MCI when utilizing the cut point of 1-2 SD below norms or premorbid estimate was largely consistent between the current sample (33.6%) and previous estimates (33%, Santangelo et al., 2015; 35%, Broeders et al., 2013; 33%, Marras et al., 2013). This cut point was recommended in the original MDS criteria. The remaining Level II cut points produced higher prevalence estimates (49.1%-87.3%), with less stringent cut points (e.g., 1 SD below norms) producing higher prevalence rates as expected. These higher rates are generally consistent with the extant literature, such as a prevalence rate of 61.8% using 2 SD below norms (Goldman et al., 2013) compared to 53.6% in the current sample.

Notably, 73.6% of presurgical patients in the current sample met criteria for MCI using Level II criteria at the cut point most concordant with clinical impressions, 1.5 SD below norms. This percentage is consistent with some previous estimates (e.g., 81%; Abboud et al., 2015; 75.7%; Gruber et al., 2019). These high rates suggest that MCI should be expected in patients seeking DBS surgery. Rather than solely presence of MCI warranting caution in surgical decision-making, perhaps examination of domain-specific impairment would provide greater clinical utility in predicting postsurgical outcomes, as the association of domains impaired at baseline with post-DBS decline has been gaining research attention (Kim et al., 2014).

Concordance calculations between clinician diagnostic impression at the time of patients' evaluations and current application of MDS criteria yielded the lowest agreement for the 1-2 SD cut point, whether below norms or below premorbid estimates. The 1-2 SD cutoff may be too restrictive, missing patients outside of that range. In contrast to Goldman et al. (2013), 2 SD below norms did not demonstrate the largest concordance with diagnostic impressions. In the current sample, 1.5 SD below norms exhibited the highest concordance, with 2 SD below norms demonstrating the second-best concordance. The 1.5 SD below norms cut point has historically been used widely in the literature, both in the context of Alzheimer's disease (Petersen et al., 1999) and PD (Pedersen et al., 2013). The continued use of this cut point is supported in the current sample.

Of those meeting criteria for MCI at 1.5 SD below norms, those with impairment in multiple cognitive domains greatly outnumbered those with single domain impairment. Although single domain, specifically in nonmemory domains, was originally believed to predominate (Litvan et al., 2011), the current reverse finding is consistent with updates to

the literature in recent years (Baiano et al., 2020; Monastero et al., 2018). Although nonmemory domains such as executive function are commonly associated with cognitive change in PD and were previously thought to predominate the cognitive profile of PD-MCI, the memory domain was most frequently impaired in MCI in the current sample. This too is in keeping with recent findings, wherein both verbal and visual delayed memory strongly differentiate normal cognition from MCI in PD (Wallace et al., 2021). Lastly, the language domain was least often impaired for those meeting MCI criteria at 1.5 SD below norms, in keeping with language measures failing to differentiate strongly between normal and impaired cognition (Wallace et al., 2021).

The visual delayed memory measure (BVMT-R) demonstrated strong classification ability of normal cognition vs. MCI at 1.5 SD below norms, as demonstrated by the most robust AUC value of all measures. A measure of executive function (D-KEFS Trail Making Test – Switching) also exhibited strong classification ability. These domains, once believed to involve separate cognitive processes and cortical areas, continue to be linked in PD. The strong performance of measures in these domains likely highlights both executively and temporally mediated processes in the PD brain and underscores the presence of both Lewy body pathology and beta-amyloid (Kalia & Lang, 2015). The Lewy pathology leading to cholinergic depletion in the hippocampus in PD-MCI may help explain the information retrieval deficits seen in PD-MCI, implicating both executive and memory processes (Liu et al., 2019). These results corroborate previous findings within pre-DBS MCI as well, with memory and executive function domains showing the most presurgical impairment. These impairments remain relevant following DBS, as amnestic MCI-multiple domain was most commonly observed post-surgically (Yágüez et al., 2014).

Ultimately, delayed visual memory demonstrated the most robust AUC, highest sensitivity and excellent specificity, and most favorable positive and negative predictive values. This finding supports the previously demonstrated strong ability of visual memory performance in differentiating normal cognition from MCI (Wallace et al., 2021). Thus, visual memory measures should be included in PD evaluations. At present, these measures are relatively underused in current research and clinical practice likely due to concerns regarding motoric impact on performance. It seems unlikely that performance on these measures or their ability to identify MCI was driven by motor difficulties and dyspraxia, as the sample was comprised of only those with PD, and associated motor difficulty, rather than healthy controls. Although there was a significant association between basic motor speed (D-KEFS Trails – Motor Speed) and delayed visual memory in the current sample ($r = .399$, $p < .001$), significant associations with motor speed were also demonstrated for nonmotor measures. This finding may reflect the association between motor and cognitive changes as the disease progresses. In clinical practice, use of measures such as the BVMT-R that include a copy trial can help mitigate concerns regarding motoric demands of visual memory measures. Copy trials, in which the patient is asked to draw the visual stimuli while viewing them after recalling them from memory, allow the delineation of motor vs. encoding or memory errors on recall trials. Confidence in visual memory measures with motor demands would be further enhanced by the creation of PD-specific norms and scoring guidelines.

4.1 Limitations

Limitations of the current study include the following: The current sample was overwhelmingly white (95.6%), limiting the findings' application to ethnically diverse

groups. Additionally, the cognitive evaluations were completed and diagnostic impressions made by four neuropsychologists, possibly affecting the consistency of the impressions. However, 109 of the 136 evaluations (80.15%) were completed by one clinician, increasing the consistency.

4.2 Conclusions

The present retrospective chart review characterizes the cognitive profile of a cohort of patients seeking DBS for PD. MDS Level I and II assessment criteria were applied, and prevalence estimates and measures' discrimination abilities examined. MCI prevalence was generally consistent with previous estimates, with Level II assessment at the 1.5 SD below norms cut point demonstrating the greatest concordance with clinical diagnostic impression. Multiple domain MCI at 1.5 SD below norms was most prevalent (64.5%) as was memory domain impairment (65.5% of those with MCI), with delayed memory performance demonstrating particularly favorable operating characteristics for MCI vs. normal cognition. Pandemic restrictions precluded the recruitment of patients for post-DBS cognitive testing to investigate cognitive outcomes for those with MCI at baseline. Future research incorporating post-surgical outcomes is needed to better inform DBS surgical planning for those with MCI and support patients and caregivers navigating cognitive changes following surgery.

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EDUCATION

2015 – 2017	**Master of Science, Psychology** University of Kentucky, Lexington KY
2010 – 2014	**Bachelor of Science, Psychology** Birmingham-Southern College, Birmingham AL

PROFESSIONAL POSITIONS HELD

July 2021 – present	**Clinical Psychology Intern** Semel Institute for Neuroscience and Human Behavior UCLA, Los Angeles CA
2020 – 2021	**Clinical Neuropsychology Practicum Student** Kentucky Neuroscience Institute: Stroke Clinic University of Kentucky, Lexington KY
2019 – 2020	**Clinical Neuropsychology Practicum Student** Robley Rex VA Medical Center Louisville KY
2019 – 2021	**Research Assistant** University of Kentucky Sanders-Brown Center on Aging Lexington KY
2018 – 2021	**Research Assistant** University of Kentucky Department of Neurology Lexington KY
2018 – 2019	**Graduate Student Therapist/Neuropsychology Student** Eastern State Hospital Lexington KY
2017 – 2018	**Clinical Neuropsychology Practicum Student** Kentucky Neuroscience Institute Lexington KY
2017 – 2018	**Graduate Student Therapist** Cardinal Hill Rehabilitation Hospital

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2016 – 2017 **Assessment Coordinator**
The Harris Center
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2016 – 2019 **Graduate Student Therapist**
The Harris Center
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SCHOLASTIC AND PROFESSIONAL HONORS

2020 – 2021 **Donovan Scholarship in Gerontology**
University of Kentucky Donovan Scholars Program

2020 **Women and Philanthropy Travel Scholarship**
University of Kentucky Sanders-Brown Center on Aging

2019 **Ashley and Ruth Mixson Psychology Award**
University of Kentucky Department of Psychology

2019 **International Neuropsychological Society Student Liaison Committee Research Award**
International Neuropsychological Society

2018 **Paul Hager Graduate Research Award**
Kentucky Psychological Association

2015-2018 **Daniel R. Reedy Quality Achievement Fellowship**
University of Kentucky Department of Psychology

2014 **Kurt Lewin/Richard McCallum Award in Psychology**
Birmingham-Southern College Department of Psychology

PROFESSIONAL PUBLICATIONS

Wallace, E. R., Harp, J. P., Van Pelt, K. L., Koehl, L. M., Caban-Holt, A. M., Anderson Mooney, A. J.,Jicha, G. A., Lightner, D. D., Robertson, W. C., Head, E., & Schmitt, F. A. (in press). Identifying dementia in Down syndrome with the Severe Impairment Battery, Brief Praxis Test, and Dementia Scale for People with Learning Disabilities. *Journal of Intellectual Disability Research*.

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